This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Set Name side by side	Query	Hit Count	Set Name result set
	DB=JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L17	L16 and l12	0	L17
L16	mediated adj electron adj transfer$4	9	L16
L15	electron adj transfer adj moeit$4	0	L15
L14	L13 and l12	14	L14
L13	(assembl$5 or selfassembl$5) near2 (layer or monolayer)	4162	L13
L12	L11 or l10 or l9 or l8 or l7 or l6 or l5 or l3 or l2 or l1	7110	L12
L11	mu adj tas	8	L11
L10	(total ot micrototal) adj analysis adj system	9	L10
L9	nanoscale or (nano adj scale)	339	L9
L8	mesoscale or (meso adj scale)	49	L8
L7	microscale or (micro adj scale)	342	L7
L6	microanaly$7 or (micro adj analy$7)	1557	L6
L5	microfabricat$7 or (micro adj fabricat$7)	907	L5
L4	microfluidic or (micro adj fluidic)	381	L4
L3	microconduit or (micro adj conduit)	23	L3
L2	microchannel or (micro adj channel)	1888	L2
L1	microchip or (micro adj chip)	2113	L1

END OF SEARCH HISTORY

WEST

Generate Collection | Print

Search Results - Record(s) 1 through 14 of 14 returned.

1. Document ID: WO 9930835 A1

L14: Entry 1 of 14 File: EPAB Jun 24, 1999

PUB-NO: WO009930835A1
DOCUMENT-IDENTIFIER: WO 9930835 A1
TITLE: METHOD AND DEVICE FOR PRODUCTION OF COMPONENTS FOR MICROFABRICATION

L14: Entry 1 of 14 File: EPAB Jun 24, 1999

PUB-NO: WO009930835A1
DOCUMENT-IDENTIFIER: WO 9930835 A1
TITLE: METHOD AND DEVICE FOR PRODUCTION OF COMPONENTS FOR MICROFABRICATION

PUBN-DATE: June 24, 1999

INT-CL (IPC): B05 B 7/06; C23 F 1/00
EUR-CL (EPC): B05B007/06

APPL-NO: IB09802056
APPL-DATE: December 16, 1998

PRIORITY-DATA: ES09702654A (December 17, 1997), US19178498A (November 13, 1998)

AB: Atomized particles within a desired size range (e.g.., 1 micron to about 5 microns) are produced from two immiscible fluids, a first fluid source containing the formulation to be atomized, and a second fluid source which is contained in a pressure chamber surrounding at least the area where the first liquid is to be provided. The invention provides methods for: the production of templates for microfabrication, such as particles that serve as templates for self-assembly of monolayers; the creation of small particles to serve as building blocks for the microassembly of objects; and the use of an atomizate to etch configurations and/or patterns onto the surface of an object by removing a selected portion of the surface.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw Desc | Image

2. Document ID: AU 200140525 A, WO 200154810 A1

L14: Entry 2 of 14 File: DWPI Aug 7, 2001

DERWENT-ACC-NO: 2001-536425
DERWENT-WEEK: 200174
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Covering set of open microchannel structures by covering structure with lid-forming material having layer of thermoglue, heating the assembly while pressing, and cooling the assembly below liquefying temperature of thermoglue

L14: Entry 2 of 14 File: DWPI Aug 7, 2001

DERWENT-ACC-NO: 2001-536425
DERWENT-WEEK: 200174
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Covering set of open microchannel structures by covering structure with lid-forming material having layer of thermoglue, heating the assembly while pressing, and cooling the assembly below liquefying temperature of thermoglue

PRIORITY-DATA: 2000SE-0000300 (January 30, 2000)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200140525 A	August 7, 2001		000	B01J019/00
WO 200154810 A1	August 2, 2001	E	023	B01J019/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 200140525A	January 22, 2001	2001AU-0040525	
AU 200140525A		WO 200154810	Based on
WO 200154810A1	January 22, 2001	2001WO-EP00653	

INT-CL (IPC): B01 J 19/00; B01 L 3/00; B29 C 65/02

AB: NOVELTY - A set of microchannel structures made of parts having different characteristics is covered by applying a side of a lid-forming material having an even layer of a thermoglue against the surface with the microchannel structures, heating the assembly while pressing the sheet material and the surface together, and permitting the structure to cool below the liquefying temperature of the thermoglue., DETAILED DESCRIPTION - Covering a set of open microchannel structures fabricated in a plastic surface of a planar substrate and made of parts that have different characteristics, involves, (a) providing a lid-forming material having on a side, an even layer of a thermoglue (such as hot-melt adhesive);, (b) applying that side of the material against the surface carrying the microchannel structures to cover the structures;, (c) heating the assembly to selectively liquefy the thermoglue while at the same time pressing the sheet material and the planar surface of the substrate together; and, (d) permitting the resulting laminate-covered microchannel structure to cool below the liquefying temperature of the thermoglue., An INDEPENDENT CLAIM is also included for a microfluidic assembly including a planar substrate and a lid-forming sheet material. The joint between the surface of the substrate and the sheet material is a thermoglue, which is possibly cured., USE - For covering open microchannel structures used in sample preparation, assay reactions and detection., ADVANTAGE - The method does not significantly change the characteristics of different part areas of the microstructures. It particularly avoids undesired inter-structure variability or inter- or intraset variability. This results to the production of sets of microchannel structures with high reproducibility.

BD

3. Document ID: JP 2000247799 A

L14: Entry 3 of 14 File: DWPI Sep 12, 2000

DERWENT-ACC-NO: 2002-219365
DERWENT-WEEK: 200228
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Thin film production comprises irradiating surface of titanium oxide substrate with UV rays through mask, and selectively absorbing organic molecules into irradiated region of substrate

L14: Entry 3 of 14 File: DWPI Sep 12, 2000

DERWENT-ACC-NO: 2002-219365
DERWENT-WEEK: 200228
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Thin film production comprises irradiating surface of titanium oxide substrate with UV rays through mask, and selectively absorbing organic molecules into irradiated region of substrate

PRIORITY-DATA: 1999JP-0046248 (February 24, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2000247799 A	September 12, 2000		009	C30B029/54

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP2000247799A	February 24, 1999	1999JP-0046248	

INT-CL (IPC): C30 B 29/54

AB: NOVELTY - Production of a thin film comprising high-density organic molecules comprises irradiating the surface of a titanium oxide substrate with ultraviolet (UV) rays through a mask comprising a material through which no UV rays pass, and selectively adsorbing organic molecules into the ultraviolet ray-irradiated region only of the substrate., USE - Production of a thin film comprising high-density organic molecules for use in protective coats, insulating films, resists for ultra-micro-fabrication, and biosensors., ADVANTAGE - The thin film has a density higher than that of conventional self-assembled mono-layers, and very high crystallinity. Any pattern is easily manufactured.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

4. Document ID: EP 1183102 A1, WO 200062931 A1, AU 200043680 A

L14: Entry 4 of 14 File: DWPI Mar 6, 2002

DERWENT-ACC-NO: 2000-665207
DERWENT-WEEK: 200224
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Microfluidic system for the electrochemical detection of target analytes, e.g. environmental pollutants, cells, hormones, nucleic acids and drugs

L14: Entry 4 of 14 File: DWPI Mar 6, 2002

DERWENT-ACC-NO: 2000-665207
DERWENT-WEEK: 200224
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Microfluidic system for the electrochemical detection of target analytes, e.g. environmental pollutants, cells, hormones, nucleic acids and drugs

PRIORITY-DATA: 1999US-0295691 (April 21, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1183102 A1	March 6, 2002	E	000	B01L003/00
WO 200062931 A1	October 26, 2000	E	114	B01L003/00
AU 200043680 A	November 2, 2000		000	B01L003/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 1183102A1	April 21, 2000	2000EP-0923580	
EP 1183102A1	April 21, 2000	2000WO-US10903	
EP 1183102A1		WO 200062931	Based on
WO 200062931A1	April 21, 2000	2000WO-US10903	
AU 200043680A	April 21, 2000	2000AU-0043680	
AU 200043680A		WO 200062931	Based on

INT-CL (IPC): B01 L 3/00; C12 Q 1/68; G01 N 33/543

AB: NOVELTY - A microfluidic system (I) for the electrochemical detection of target analytes, is new., DETAILED DESCRIPTION - A microfluidic system (I) for the detection of a target analyte in a sample comprising a solid support, comprising:, (1) a sample inlet port;, (2) a sample handling well comprising at least 1 well port;, (3) a first microchannel to allow fluid contact between the sample inlet port and the sample handling port;, (4) a detection module, comprising:, (a) a detection electrode;, (b) a self assembled monolayer;, (c) a binding ligand; and, (d) a detection port inlet port to receive the sample; and, (5) a second microchannel to allow fluid contact between the sample handling well port and the detection inlet port., An INDEPENDENT CLAIM is also included for a method (II) for the detection of a target analyte in a sample, comprising:, (A) introducing the sample to a sample inlet port of a microfluidic device comprising a solid support, comprising:, (I) at least 1 sampling handling well comprising a well inlet port and a well outlet port;, (II) a first microchannel to allow fluid contact between thew sample inlet port and the sample handling well;, (III) a detection electrode comprising:, (1) a self assembled monolayer;, (2) a binding ligand; and, (3) a detection port inlet port to receive the sample; and, (IV) a second microchannel to allow fluid contact between the sample handling well and the detection inlet port; and, (B) detecting the presence of the target analyte in the sample., USE - (I) may be used to detect target analytes such as environmental pollutants (e.g. pesticides, toxins and insecticides), chemicals (e.g. solvents, polymers and organic materials), therapeutic molecules (e.g. therapeutic and abused drugs), biomolecules (e.g. hormones, cytotoxins, proteins, lipids, carbohydrates, antigens and receptors or their ligands), whole cells (e.g. pathogenic bacteria and tumor cells), viruses (e.g. retroviruses and herpes viruses), and other molecules including nucleic acids, enzymes, antibodies, growth factors and cytokines., ADVANTAGE - (I) Is small in size improving sensitivity and reducing equipment and reagent costs, and allows electronic detection of the analytes., DESCRIPTION OF DRAWING(S) - The drawing shows a microfluidic system for the electrochemical detection of target analytes., Solid support 5, Inlet port 10, Microchannels 15, 20, Storage module 25, Detection module 30, Electrodes 35, 20A

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Clip Img | Image

5. Document ID: US 6100107 A

L14: Entry 5 of 14 File: DWPI Aug 8, 2000

DERWENT-ACC-NO: 2000-542427
DERWENT-WEEK: 200049
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Preparation of microchannel/sensor-integrated assembly involves integrating a microchannel and a sensor in one single substrate

L14: Entry 5 of 14 File: DWPI Aug 8, 2000

DERWENT-ACC-NO: 2000-542427
DERWENT-WEEK: 200049
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Preparation of microchannel/sensor-integrated assembly involves integrating a microchannel and a sensor in one single substrate

PRIORITY-DATA: 1998US-0137447 (August 6, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6100107 A	August 8, 2000		005	H01L021/302

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 6100107A	August 6, 1998	1998US-0137447	

INT-CL (IPC): H01 L 21/302

AB: NOVELTY - An integrated assembly of a microchannel and an element is prepared by integrating the microchannel and the sensor in one single substrate., DETAILED DESCRIPTION - Preparation of an integrated assembly of a microchannel and a sensor involves providing a sensor (6) between a substrate (1) and a sacrificial layer (11). Two protection layers (2, 10) are prepared to isolate the sensor from its ambient environment. The sacrificial layer defines an area to be etched off such that a microchannel can be formed. A coating layer (15) with etching windows is then provided on the sacrificial layer and the assembly is etched in an etchant to etch off the sacrificial layer and an area of the substrate beneath the sacrificial layer., USE - The method is used for preparing a microchannel and sensor integrated assembly., ADVANTAGE - The method does not require bonding processes., DESCRIPTION OF DRAWING(S) - The figure shows a microchannel-sensor assembly., Substrate 1, Protection layers 2, 10, Sensor 6, Sacrificial layer 11, Coating layer 15

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Clip Img | Image

6. Document ID: WO 9851999 A1, AU 9873792 A, US 6154226 A

L14: Entry 6 of 14 File: DWPI Nov 19, 1998

DERWENT-ACC-NO: 1999-009902
DERWENT-WEEK: 199901
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Multi-print array that incorporates electro-hydrodynamic device to selectively dispense stored fluid - has drivers which dispense stored fluids when appropriate control signals are received, to selectively dispense stored fluids onto surface of receptor

L14: Entry 6 of 14 File: DWPI Nov 19, 1998

DERWENT-ACC-NO: 1999-009902
DERWENT-WEEK: 199901
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Multi-print array that incorporates electro-hydrodynamic device to selectively dispense stored fluid - has drivers which dispense stored fluids when appropriate control signals are received, to selectively dispense stored fluids onto surface of receptor

PRIORITY-DATA: 1997US-0939769 (September 29, 1997), 1997US-046292P (May 13, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9851999 A1	November 19, 1998	E	035	G01D015/14
AU 9873792 A	December 8, 1998		000	G01D015/14
US 6154226 A	November 28, 2000		000	G01D015/16

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9851999A1	May 12, 1998	1998WO-US09579	
AU 9873792A	May 12, 1998	1998AU-0073792	
AU 9873792A		WO 9851999	Based on
US 6154226A	May 13, 1997	1997US-046292P	Provisional
US 6154226A	September 29, 1997	1997US-0939769	

INT-CL (IPC): G01 D 15/14; G01 D 15/16; H02 K 44/02

AB: The print array (240 comprises number of layers or cartridges, e.g. reservoir layer (410), distribution layer (420) and dispensing layers (430). The reservoir layers carry reservoirs (412) filled with types of pigments, bonded to dispensing layers, in turn which are bonded to distribution layers that contain channels (422) for directing fluid from reservoir layer to the dispensing layers. The dispensing layer contains individually addressable micropumps (434), e.g. EHD micropumps, and orifices for dispensing the pigments onto a receptor., The three assembled layers form a single unit, a print array, based on high-density microfluidic array and reservoir system with electronic drivers to control the micropumps, which serve as droplets formation and dispensing mechanism. The controller which controls the print operation of the printer is designed to receive print commands from different devices, e.g. a computer, imaging device or digital camera., ADVANTAGE - Use of EHD phenomenon involves various forces such as electrokinetic (Coulomb) forces like electrophoretic and electro-osmotic forces, Kelvin polarisation force, dielectric and electrostatic force, ensures accurate dispensing of amounts of fluid by micropump within each microchannel., The print array (240 comprises number of layers or cartridges, e.g. reservoir layer (410), distribution layer (420) and dispensing layers (430). The reservoir layers carry reservoirs (412) filled with types of pigments, bonded to dispensing layers, in turn which are bonded to distribution layers that contain channels (422) for directing fluid from reservoir layer to the dispensing layers. The dispensing layer contains individually addressable micropumps (434), e.g. EHD micropumps, and orifices for dispensing the pigments onto a receptor., The three assembled layers form a single unit, a print array, based on high-density microfluidic array and reservoir system with electronic drivers to control the micropumps, which serve as droplets formation and dispensing mechanism. The controller which controls the print operation of the printer is designed to receive print commands from different devices, e.g. a computer, imaging device or digital camera., ADVANTAGE - Use of EHD phenomenon involves various forces such as electrokinetic (Coulomb) forces like electrophoretic and electro-osmotic forces, Kelvin polarisation force, dielectric and electrostatic force, ensures accurate dispensing of amounts of fluid by micropump within each microchannel.

7. Document ID: RU 2118997 C1

L14: Entry 7 of 14 File: DWPI Sep 20, 1998

DERWENT-ACC-NO: 2000-114919
DERWENT-WEEK: 200010
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Method of manufacturing polycrystalline diamond layers

L14: Entry 7 of 14 File: DWPI Sep 20, 1998

DERWENT-ACC-NO: 2000-114919
DERWENT-WEEK: 200010
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Method of manufacturing polycrystalline diamond layers

PRIORITY-DATA: 1997RU-0101049 (January 24, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
RU 2118997 C1	September 20, 1998		000	C30B029/04

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
RU 2118997C1	January 24, 1997	1997RU-0101049	

INT-CL (IPC): B01 J 3/06; C01 B 31/06; C30 B 29/04

AB: NOVELTY - Graphite-containing substance and heat-conducting material layers are assembled into packet in which graphite-containing layer is in contact with heat- conducting layers on its both sides. Packet is placed into ampoule, cooled from 189-160 deg. C, and then affected by detonation pressure from 40 - 50 GPa for 2-4 minutes., USE - Artificial diamonds technology. Product is appropriate for use in electronic engineering, precision mechanics, and microfabrication technology., ADVANTAGE - Simplified process and reduced production cost.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Drawi Desc | Image

8. Document ID: DE 19710716 C2, WO 9841076 A2, DE 19710716 A1

L14: Entry 8 of 14 File: DWPI May 10, 2001

DERWENT-ACC-NO: 1998-507161
DERWENT-WEEK: 200126
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Microstructured heat-sink for high-performance laser diode or diode-pumped solid-state laser - has microchannel plate, intermediate plate and collector plate assembled with individual layers between base and cover plates

L14: Entry 8 of 14 File: DWPI May 10, 2001

DERWENT-ACC-NO: 1998-507161
DERWENT-WEEK: 200126
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Microstructured heat-sink for high-performance laser diode or diode-pumped solid-state laser - has microchannel plate, intermediate plate and collector plate assembled with individual layers between base and cover plates

PRIORITY-DATA: 1997DE-1010716 (March 14, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
DE 19710716 C2	May 10, 2001		000	H01S005/024
WO 9841076 A2	September 17, 1998	G	020	H05K007/20
DE 19710716 A1	September 24, 1998		000	H01S003/043

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
DE 19710716C2	March 14, 1997	1997DE-1010716	
WO 9841076A2	March 16, 1998	1998WO-DE00786	
DE 19710716A1	March 14, 1997	1997DE-1010716	

INT-CL (IPC): H01 L 23/473; H01 S 3/043; H01 S 5/024; H05 K 7/20

AB: The heat-sink has a number of individual layers, at least one microchannel plate (8) with a series of microchannels and a distribution channel, at least one intermediate plate (3-7) with a number of connecting channels and a collector plate (2) with a number of collector channels, assembled with the individual layers between a base plate (1) and a cover plate (13), to provide sealed cooling channels., A cooling medium for feeding through the latter channels is supplied to the heat sink via an inlet and discharged via an outlet, the intermediate plate forming a graded and/or skewed transitional structure between the inlet and outlet openings., ADVANTAGE - Increased cooling medium flow for efficient dissipation of waste heat.

9. Document ID: US 6306584 B1, WO 9831839 A2, AU 9859265 A, EP 981643 A2

L14: Entry 9 of 14 File: DWPI Oct 23, 2001

DERWENT-ACC-NO: 1998-414129
DERWENT-WEEK: 200165
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Probing of molecules at surfaces - by passing electron between biological species, used in e.g. test assays, biosensing applications or disease detection

L14: Entry 9 of 14 File: DWPI Oct 23, 2001

DERWENT-ACC-NO: 1998-414129
DERWENT-WEEK: 200165
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Probing of molecules at surfaces - by passing electron between biological species, used in e.g. test assays, biosensing applications or disease detection

PRIORITY-DATA: 1997US-0843623 (April 10, 1997), 1997US-0786153 (January 21, 1997), 1997US-0804883 (February 24, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6306584 B1	October 23, 2001		000	C12Q001/68
WO 9831839 A2	July 23, 1998	E	102	C12Q001/68
AU 9859265 A	August 7, 1998		000	C12Q001/68
EP 981643 A2	March 1, 2000	E	000	C12Q001/68

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 6306584B1	January 21, 1997	1997US-0786153	CIP of
US 6306584B1	February 24, 1997	1997US-0804883	CIP of
US 6306584B1	April 10, 1997	1997US-0843623	
WO 9831839A2	January 21, 1998	1998WO-US01144	
AU 9859265A	January 21, 1998	1998AU-0059265	
AU 9859265A		WO 9831839	Based on
EP 981643A2	January 21, 1998	1998EP-0902663	
EP 981643A2	January 21, 1998	1998WO-US01144	
EP 981643A2		WO 9831839	Based on

INT-CL (IPC): C12 Q 1/68; G01 N 33/53

AB: (A) A method is claimed comprising:, (a) introducing an electron into a first biological species that is one of a pair of biological binding partners defined by the first biological species and a second biological species;, (b) passing the electron through the first species and into the second species, and, (c) removing the electron from the second species., Also claimed are:, (B) a method comprising passing an electron through a biological species linked to a self-assembled monolayer-forming species immobilised at a surface of an article;, (C) a method comprising:, (a) providing a first biological species that is linked to a surface of a first article via a self-assembled monolayer and a second biological species that is linked to the surface via a self-assembled monolayer, and, (b) passing an electron through the first biological species while the second biological species does not pass an electron;, (D) a method comprising:, (a) providing a first biological species immobilised at a surface of a first article and a second biological species immobilised to the surface of the first article, and, (b) as (C)(b);, (E) an article comprising a first electrode having a surface, a second electrode having a surface, an electrical circuit connecting the first and second electrodes, a first biological species immobilised at a surface of the first electrode, and a biological binding partner of the first biological species immobilised at the second electrode;, (F) a method comprising determining the interaction of a first molecule with a second molecule by detecting a change in electronic configuration of the second molecule due to interaction of the second molecule with the first molecule;, (G) a method comprising:, (a) immobilising a protein at a surface;, (b) inducing a change in the conformation of the protein at the surface, and, (c) detecting the change in conformation;, (H) a method comprising:, (a) providing a protein;, (b) exposing the protein to a prion or associated cofactor, and, (c) determining a change in conformation of the protein induced by exposure of the protein to the prion, and, (I) a method comprising determining a disease state involving mis-folded protein in a physiological sample of a living mammal., USE - The methods and products can be used for studying molecular reactions at surfaces. They can be used in test assays such as a diagnostic procedure, analytical procedure, microanalytical procedure, forensic analysis, pharmacokinetic study, cell sorting procedure, affinity chromatogram, industrial or laboratory recovery or in the analysis of one or more species such as toxins, catalysts, starting materials or products or immunoassays., The methods and products can also be used in biosensing applications such as drug screening, environmental monitoring, medical diagnostics, quality control in the pharmaceutical and food industries, and other areas in which it is advantageous to sensitively determine biological binding between partners. The methods and products can also be used for the detection of disease states involving mis-folded forms of normal proteins, e.g. transmissible prion diseases (TSE's), such as bovine spongiform encephalopathy (mad cow disease), scrapie in sheep or in humans, Creutzfeldt-Jacob disease, fatal familial insomnia, Gerstmann-Straussler-Sheinker disease or kuru., (A) A method is claimed comprising:, (a) introducing an electron into a first biological species that is one of a pair of biological binding partners defined by the first biological species and a second biological species;, (b) passing the electron through the first species and into the second species, and, (c) removing the electron from the second species., Also claimed are:, (B) a method comprising passing an electron through a biological species linked to a self-assembled monolayer-forming species immobilised at a surface of an article;, (C) a

method comprising:, (a) providing a first biological species that is linked to a surface of a first article via a self-assembled monolayer and a second biological species that is linked to the surface via a self-assembled monolayer, and, (b) passing an electron through the first biological species while the second biological species does not pass an electron;, (D) a method comprising:, (a) providing a first biological species immobilised at a surface of a first article and a second biological species immobilised to the surface of the first article, and, (b) as (C)(b);, (E) an article comprising a first electrode having a surface, a second electrode having a surface, an electrical circuit connecting the first and second electrodes, a first biological species immobilised at a surface of the first electrode, and a biological binding partner of the first biological species immobilised at the second electrode;, (F) a method comprising determining the interaction of a first molecule with a second molecule by detecting a change in electronic configuration of the second molecule due to interaction of the second molecule with the first molecule;, (G) a method comprising:, (a) immobilising a protein at a surface;, (b) inducing a change in the conformation of the protein at the surface, and, (c) detecting the change in conformation;, (H) a method comprising:, (a) providing a protein;, (b) exposing the protein to a prion or associated cofactor, and, (c) determining a change in conformation of the protein induced by exposure of the protein to the prion, and, (I) a method comprising determining a disease state involving mis-folded protein in a physiological sample of a living mammal., USE - The methods and products can be used for studying molecular reactions at surfaces. They can be used in test assays such as a diagnostic procedure, analytical procedure, microanalytical procedure, forensic analysis, pharmacokinetic study, cell sorting procedure, affinity chromatogram, industrial or laboratory recovery or in the analysis of one or more species such as toxins, catalysts, starting materials or products or immunoassays., The methods and products can also be used in biosensing applications such as drug screening, environmental monitoring, medical diagnostics, quality control in the pharmaceutical and food industries, and other areas in which it is advantageous to sensitively determine biological binding between partners. The methods and products can also be used for the detection of disease states involving mis-folded forms of normal proteins, e.g. transmissible prion diseases (TSE's), such as bovine spongiform encephalopathy (mad cow disease), scrapie in sheep or in humans, Creutzfeldt-Jacob disease, fatal familial insomnia, Gerstmann-Straussler-Sheinker disease or kuru.

10. Document ID: DE 69707853 E, WO 9733737 A1, AU 9723247 A, EP 894043 A1, AU 723909 B, EP 894043 B1

L14: Entry 10 of 14 File: DWPI Dec 6, 2001

DERWENT-ACC-NO: 1997-489228
DERWENT-WEEK: 200203
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Creating patterns on substrate surface for e.g. combinatorial chemical synthesis - using mould with surface indentations positioned on the surface and to which e.g. inorganic compound precursor or biochemical reagent is supplied

L14: Entry 10 of 14 File: DWPI Dec 6, 2001

DERWENT-ACC-NO: 1997-489228
DERWENT-WEEK: 200203
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Creating patterns on substrate surface for e.g. combinatorial chemical synthesis - using mould with surface indentations positioned on the surface and to which e.g. inorganic compound precursor or biochemical reagent is supplied

PRIORITY-DATA: 1996US-0616929 (March 15, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
DE 69707853 E	December 6, 2001		000	B29C037/00
WO 9733737 A1	September 18, 1997	E	066	B29C037/00
AU 9723247 A	October 1, 1997		000	B29C037/00
EP 894043 A1	February 3, 1999	E	000	B29C037/00
AU 723909 B	September 7, 2000		000	B29C037/00
EP 894043 B1	October 31, 2001	E	000	B29C037/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
DE 69707853E	March 14, 1997	1997DE-0607853	
DE 69707853E	March 14, 1997	1997EP-0915950	
DE 69707853E	March 14, 1997	1997WO-US04005	
DE 69707853E		EP 894043	Based on
DE 69707853E		WO 9733737	Based on
WO 9733737A1	March 14, 1997	1997WO-US04005	
AU 9723247A	March 14, 1997	1997AU-0023247	
AU 9723247A		WO 9733737	Based on
EP 894043A1	March 14, 1997	1997EP-0915950	
EP 894043A1	March 14, 1997	1997WO-US04005	
EP 894043A1		WO 9733737	Based on
AU 723909B	March 14, 1997	1997AU-0023247	
AU 723909B		AU 9723247	Previous Publ.
AU 723909B		WO 9733737	Based on
EP 894043B1	March 14, 1997	1997EP-0915950	
EP 894043B1	March 14, 1997	1997WO-US04005	
EP 894043B1		WO 9733737	Based on

INT-CL (IPC): B29 C 37/00; B29 C 39/24

AB: A pattern of an inorganic species (A) is produced in a region close to a substrate surface (SS) by: (1) applying to an article with a pattern of surface indentations a pattern (corresponding to the indentations) of a fluid precursor (B) of (A) and (2) allowing (B) to harden at a first region of SS, in the specified pattern and in an area having a lateral dimension < 1 mm (especially < 20 mu m), while leaving a second, contiguous region of SS free of (A). A similar method can be used for materials other than (B), i.e. a suspension of particles in a fluid carrier; an agent that promotes deposition of metal; chelating agents; chemically reactive agent coupled to particles, or biochemically active agent., When a suspension of particles (particularly microbeads) is used, this is deposited on the first region and the carrier allowed to dissipate, depositing the particles on the first region of SS. A similar method is used for deposition of metals. Transfer from the patterned surface to SS is almost instantaneous and the article may have two separate indented regions to produce two treated regions on SS, with an intervening untreated region. A preferred biochemical agent is a binding partner which may include a polyamino acid tag for immobilisation to a metal ion, coordinated to a chelating agent that is itself immobilised on SS., USE - The method is used to transfer specific agents to particular regions of SS, particularly for use in synthesis of combinatorial libraries at the micro- or nano-scales, but more generally for performing a wide range of chemical reactions. The treated SS may also be used to produce self-assembled monolayers. Typical (bio)chemical agents are e.g. prepolymers, inorganic salts, ceramics, metals, catalysts and colloidal active agents., ADVANTAGE - The method provides convenient, inexpensive, simple and reproducible micropatterning of SS., A pattern of an inorganic species (A) is produced in a region close to a substrate surface (SS) by: (1) applying to an article with a pattern of surface indentations a pattern (corresponding to the indentations) of a fluid precursor (B) of (A) and (2) allowing (B) to harden at a first region of SS, in the specified pattern and in an area having a lateral dimension < 1 mm (especially < 20 mu m), while leaving a second, contiguous region of SS free of (A). A similar method can be used for materials other than (B), i.e. a suspension of particles in a fluid carrier; an agent that promotes deposition of metal; chelating agents; chemically reactive agent coupled to particles, or biochemically active agent., When a suspension of particles (particularly microbeads) is used, this is deposited on the first region and the carrier allowed to dissipate, depositing the particles on the first region of SS. A similar method is used for deposition of metals. Transfer from the patterned surface to SS is almost instantaneous and the article may have two separate indented regions to produce two treated regions on SS, with an intervening untreated region. A preferred biochemical agent is a binding partner which may include a polyamino acid tag for immobilisation to a metal ion, coordinated to a chelating agent that is itself immobilised on SS., USE - The method is used to transfer specific agents to particular regions of SS, particularly for use in synthesis of combinatorial libraries at the micro- or nano-scales, but more generally for performing a wide range of chemical reactions. The treated SS may also be used to produce self-assembled monolayers. Typical (bio)chemical agents are e.g. prepolymers, inorganic salts, ceramics, metals, catalysts and colloidal active agents., ADVANTAGE - The method provides convenient, inexpensive, simple and reproducible micropatterning of SS.

11. Document ID: WO 9725531 A1, AU 9713586 A

L14: Entry 11 of 14 File: DWPI Jul 17, 1997

DERWENT-ACC-NO: 1997-372935
DERWENT-WEEK: 199734
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Microsized pump formed as channel in substrate with vibratable wall - with sonic generator producing elastic waves travelling in single direction along channel

L14: Entry 11 of 14 File: DWPI Jul 17, 1997

DERWENT-ACC-NO: 1997-372935
DERWENT-WEEK: 199734
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Microsized pump formed as channel in substrate with vibratable wall - with sonic generator producing elastic waves travelling in single direction along channel

PRIORITY-DATA: 1996US-009665P (January 5, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9725531 A1	July 17, 1997	E	047	F04B019/24
AU 9713586 A	August 1, 1997		000	F04B019/24

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9725531A1	January 6, 1997	1997WO-US00076	
AU 9713586A	January 6, 1997	1997AU-0013586	
AU 9713586A	January 6, 1997	1997WO-US00076	
AU 9713586A		WO 9725531	Based on

INT-CL (IPC): F04 B 17/00; F04 B 19/24

AB: A microsized pump is formed in a substrate (12) in which is created a channel (14) having a vibratable wall (16). A sonic energy generator (24) is in energy transmitting relation to the vibratable wall. It generates elastic waves which travel along the length of the channel. The waves are limited so that they travel in a single direction., USE - The pump can be used to move material along the channel so that chemical and biological analysis can be effected on a micro scale. The channel may form a chromatographic column with the walls of the channel coated with a stationary phase, e.g. a polymer or a self-assembled monolayer., ADVANTAGE - The pump construction is simple compared to most micropumps. It has no moving parts. In contrast to diaphragm pumps, the mechanism that induces fluid motion is distributed over the length of the channel. Also the elastic waves act on the fluid very close to its interface with the wall. Thus the pump moves fluids down long, shallow and narrow tunnels without incurring the pressure limitations of discrete pumps.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Clip Img | Image

12. Document ID: WO 9706468 A2, WO 9706468 A3, AU 9667524 A

L14: Entry 12 of 14 File: DWPI Feb 20, 1997

DERWENT-ACC-NO: 1997-212481
DERWENT-WEEK: 199719
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Prodn. of micro-scale and nano-scale - uses multilayer vetoing, polymerisation methods, casting, injection moulding, embossing or curing prepolymer solns.

L14: Entry 12 of 14 File: DWPI Feb 20, 1997

DERWENT-ACC-NO: 1997-212481
DERWENT-WEEK: 199719
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Prodn. of micro-scale and nano-scale - uses multilayer vetoing, polymerisation methods, casting, injection moulding, embossing or curing prepolymer solns.

PRIORITY-DATA: 1995US-0509020 (July 28, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9706468 A2	February 20, 1997	E	083	G03C000/00
WO 9706468 A3	July 31, 1997		000	G03C000/00
AU 9667524 A	March 5, 1997		000	G03F007/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9706468A2	July 26, 1996	1996WO-IB00912	
WO 9706468A3	July 26, 1996	1996WO-IB00912	
AU 9667524A	July 26, 1996	1996AU-0067524	
AU 9667524A		WO 9706468	Based on

INT-CL (IPC): G03 C 0/00; G03 F 7/00

AB: Prodn. of microscale or nano-scale devices comprises the use of replicated patterned relief surfaces and a mask forming step selected from:, (a) multilayer vetoing of self-assembly monolayer patterns on metallic films;, (b) polymerisation of resist from patterned initiator cpd. regions;, (c) casting of polymeric resist patterns on surfaces;, (d) injection moulding of resist precursors;, (e) embossing of a preformed resist film followed by a mild etch to eliminate reduced thickness regions, and, (f) curing of prepolymer solns. wetting underlying patterns., USE - The methods can be used for the generation of masking patterns for etch control and diffusion barrier formation in semiconductor fabrication, micro-fluidics fabrication and micro-electromechanical systems (MEMs), patterned chemical synthesis and copolymer synthesis, the formation of patterned molecular monolayers and multilayers, replication of chemical patterns and fabrication of microstructural and nano-structural materials., ADVANTAGE - The methods can provide for a combination of large scale, rapid pattern prodn. and pattern fidelity.

13. Document ID: US 5514501 A

L14: Entry 13 of 14 File: DWPI May 7, 1996

DERWENT-ACC-NO: 1996-238747
DERWENT-WEEK: 199624
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Creating two dimensional pattern of thiolate cpds. on substrate - by oxidising regions of assembled monolayer of one thiol then exchanging oxidised cpds. with second

thiol, esp. used for selective binding of e.g. proteins, DNA, for biosensor(s) and immunoassays

L14: Entry 13 of 14 File: DWPI May 7, 1996

DERWENT-ACC-NO: 1996-238747
DERWENT-WEEK: 199624
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Creating two dimensional pattern of thiolate cpds. on substrate - by oxidising regions of assembled monolayer of one thiol then exchanging oxidised cpds. with second thiol, esp. used for selective binding of e.g. proteins, DNA, for biosensor(s) and immunoassays

PRIORITY-DATA: 1994US-0255961 (June 7, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5514501 A	May 7, 1996		012	G03F007/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 5514501A	June 7, 1994	1994US-0255961	

INT-CL (IPC): G03 C 5/16; G03 F 7/00

AB: A two-dimensional distribution (pattern) of thiolate cpds. in a self-assembled monolayer (SAM), formed on a substrate is created by: (1) illuminating a SAM made from a first thiolate (Ia) in presence of O2 with high frequency electromagnetic radiation according to a predetermined pattern; then (2) immersing the substrate in a soln. of a second thiolate (Ib) so that oxidised (Ia) in the illuminated regions are replaced by (Ib). Opt. the (Ia)-(Ib) SAM is then immersed in a soln. of a biological cpd. (A) that preferentially adsorbs onto one of (Ia) and (Ib) for attachment of (A) to specific areas of the surface., USE - The patterns can be used to bind proteins, enzymes, DNA or cells at specific locations, e.g. for use in biosensors, diagnostic immunoassays, DNA assay or sequencing, pharmacological or toxicological tests or cell growth studies. Partic. applications are miniaturised multi-binding sensors for use in blood vessels or single cells, miniaturised DNA sequencers supported on microchips or (using the patterns as resists for selective chemical etching) to make individually addressable microelectrodes., ADVANTAGE - In the pattern the line spacing can be less than 100 mu; photopatterning involves no physical contact with the sample (so avoiding deformation) and no photoactive pendant groups are required.

14. Document ID: BE 905604 A, CH 670920 A, DE 3640723 A, FR 2596200 A, GB 2188477 A, GB 2188477 B, JP 62229741 A, NL 8602787 A, US 4730141 A

L14: Entry 14 of 14 File: DWPI Feb 2, 1987

DERWENT-ACC-NO: 1987-050386
DERWENT-WEEK: 198708
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Infrared imaging tube using reflection from photocathode - has image radiation

impinging on optoelectronic mosaic to locally stimulate cathode to generate representative electron beam

L14: Entry 14 of 14 File: DWPI Feb 2, 1987

DERWENT-ACC-NO: 1987-050386
DERWENT-WEEK: 198708
COPYRIGHT 2002 DERWENT INFORMATION LTD

TITLE: Infrared imaging tube using reflection from photocathode - has image radiation impinging on optoelectronic mosaic to locally stimulate cathode to generate representative electron beam

PRIORITY-DATA: 1986US-0842298 (March 21, 1986)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
BE 905604 A	February 2, 1987		009	
CH 670920 A	July 14, 1989		000	
DE 3640723 A	October 1, 1987		000	
FR 2596200 A	September 25, 1987		000	
GB 2188477 A	September 30, 1987		000	
GB 2188477 B	August 8, 1990		000	
JP 62229741 A	October 8, 1987		000	
NL 8602787 A	October 16, 1987		000	
US 4730141 A	March 8, 1988		004	

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
BE 905604A	October 15, 1986	1986BE-0905604	
DE 3640723A	November 28, 1986	1986DE-3640723	
GB 2188477A	March 4, 1986	1986GB-0005031	
JP62229741A	November 28, 1986	1986JP-0284074	
US 4730141A	March 21, 1986	1986US-0842298	

INT-CL (IPC): G02B 23/12; H01J 29/89; H01J 31/50; H01J 43/24; H01L 31/14

AB: The metal case (12) of the imaging tube has a partition (18) between a cooling chamber (14) and an evacuated zone (16) which has an infra red window (20) at one end and a convex lens (22) mid-way. This carries at its centre an electronic lens (26) backed by a fluorescent layer (64) and image intensifier (32). A mosaic of photodiodes (44) is mounted on a common electrode (42) in front of the partition (18), each having an individual electrode (46) on its front surface, with a photocathode (48) laid over all., A control grid (50) placed in front inhibits the passage of electrons stimulated in the photocathode by an internal infra red source (52). When image radiation (60) strikes the mosaic, individual photodiodes change potential and hence also the local photocathode area. This allows an electron beam in image form to pass the grid and reach the lens and fluorescent layer assembly for conversion to visible light. Viewing is effected via an internal prism (36) and side window (38)., ADVANTAGE - Reflection technique increases efficiency by facilitating cooling and potential regulation of photocathode zone., An imaging tube for imaging light energy comprising: a housing; a first window; a second window; a reflective photocathode within the housing adapted to emit electrons in response to light energy incident thereon; a conversion element for converting electrons to light energy; and an optical element; said first window and said second window being mounted in said housing to define therewith a vacuum-tight zone and to transmit therethrough respectively a first set and a second set of rays of light energy, said first set being said light energy to be imaged; said first window being arranged to transmit said first set along a first axis and said second window being arranged to transmit said second set along a second axis, said first axis intersecting said second axis at an angle of less than 180 deg; said conversion element being mounted to receive said electrons and to provide said second set; said optical element being mounted in said housing and including a centrally discontinuous portion in which said conversion element is mounted; and said optical element being orientated with respect to said first window and said photocathode so that said first set is directed by said optical element onto said photocathode., Electrons (62) leaving a reflective photocathode (48) are focused by an electron lens (28) onto the concavo surface of a microchannel plate (30) in which the signal is amplified. It goes through a vacuum gap onto phosphor layer (34) coated on the concavo surface of a fibre optic bundle (32) the phosphor converting the electrons to visible light which is turned by a prism (36) to be viewed through a window (38). Distortion is modified by the fibre optic bundle., ADVANTAGE - Temperature and electrical potential of photocathode may be easily controlled. Cooling may be direct and efficient. B(4pp)o

Generate Collection | Print

Terms	Documents
L13 and l12	14

Display Format: TI,DAT Change Format

Previous Page Next Page

WEST

Help | Logout | Interrupt

Main Menu | Search Form | Posting Counts | Show S Numbers | Edit S Numbers | Preferences | Cases

Search Results -

Terms	Documents
L16 and l12	0

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Search: L17

Refine Search

Recall Text | Clear

Search History

DATE: Friday, May 17, 2002 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
	DB=JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L17	L16 and l12	0	L17
L16	mediated adj electron adj transfer$4	9	L16
L15	electron adj transfer adj moeit$4	0	L15
L14	L13 and l12	14	L14
L13	(assembl$5 or selfassembl$5) near2 (layer or monolayer)	4162	L13
L12	L11 or l10 or l9 or l8 or l7 or l6 or l5 or l3 or l2 or l1	7110	L12
L11	mu adj tas	8	L11
L10	(total ot micrototal) adj analysis adj system	9	L10
L9	nanoscale or (nano adj scale)	339	L9
L8	mesoscale or (meso adj scale)	49	L8
L7	microscale or (micro adj scale)	342	L7
L6	microanaly$7 or (micro adj analy$7)	1557	L6
L5	microfabricat$7 or (micro adj fabricat$7)	907	L5
L4	microfluidic or (micro adj fluidic)	381	L4
L3	microconduit or (micro adj conduit)	23	L3
L2	microchannel or (micro adj channel)	1888	L2
L1	microchip or (micro adj chip)	2113	L1

END OF SEARCH HISTORY

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L24	l17 not l19	94	L24
L23	l15 not l19	94	L23
L22	L21 and l12	26	L22
L21	electron adj transfer adj moiet$4	43	L21
L20	electro adj transfer adj moiet$4	0	L20
L19	L18 and l12	26	L19
L18	((assembl$6 or selfassembl$6) near2 (layer or monolayer)) same detect$4	236	L18
L17	l13 not l16	110	L17
L16	l13 not l15	10855	L16
L15	L14 and (204/$.ccls. or 422/$.ccls. or 435/$.ccls. or 436/$.ccls.)	110	L15
L14	L13 and l12	320	L14
L13	(assembl$6 or selfassembl$6) near2 (layer or monolayer)	10965	L13
L12	L11 or l10 or l9 or l8 or l7 or l6 or l5 or l3 or l2 or l1	16927	L12
L11	mu adj tas	22	L11
L10	(total or micrototal) adj analysis adj system	38	L10
L9	nanoscale or (nano adj scale)	679	L9
L8	mesoscale or (meso adj scale)	106	L8
L7	microscale or (micro adj scale)	1529	L7
L6	microfluidic or (micro adj fluidic)	1112	L6
L5	microanaly$6 or (micro adj analy$6)	5672	L5
L4	microfabricat$6 or (micro adj fabricat$6)	2840	L4
L3	microconduit or (micro adj conduit)	34	L3
L2	microchannel or (micro adj channel)	4036	L2
L1	microchip or (micro adj chip)	4773	L1

END OF SEARCH HISTORY

WEST

Number of documents to display is limited to 50 for TI,DATE,KWIC format

Generate Collection | Print

Search Results - Record(s) 1 through 26 of 26 returned.

☒ 1. Document ID: US 6376268 B1

L19: Entry 1 of 26 File: USPT Apr 23, 2002

US-PAT-NO: 6376268
DOCUMENT-IDENTIFIER: US 6376268 B1

TITLE: Optoelectronic assembly and method of making the same

L19: Entry 1 of 26 File: USPT Apr 23, 2002

US-PAT-NO: 6376268
DOCUMENT-IDENTIFIER: US 6376268 B1

TITLE: Optoelectronic assembly and method of making the same

DATE-ISSUED: April 23, 2002

US-CL-CURRENT: 438/26; 257/433, 257/99, 438/27

APPL-NO: 9/ 334146
DATE FILED: June 15, 1999

PARENT-CASE:

This Appln is a Div of Ser. No. 09/003,114 filed Jan. 6, 1998, U.S. Pat. No. 5,997,567.

L19: Entry 1 of 26 File: USPT Apr 23, 2002

DOCUMENT-IDENTIFIER: US 6376268 B1
TITLE: Optoelectronic assembly and method of making the same

Brief Summary Paragraph Right (20):
These objects and advantages are achieved by an optoelectronic assembly having an insulating substrate with a planar surface and a metal layer bonded to the planar surface such that selected regions of the substrate are exposed and a step is produced between the substrate and a top surface of the metal layer. An active optical device such as a diode laser, optical amplifier, optical modulator, light detector or any other device is mounted on the metal layer. The active device has a first optical axis and in this arrangement this axis is parallel to the substrate. In addition, the metal layer provides an electrical path to the active device. It is essential for the optoelectronic assembly that the metal layer have a well-defined thickness. This thickness is selected such that the heat generated by the active device is dissipated, the substrate does not interfere with the propagation of light along the first optical axis, and such that the in-plane coefficient of thermal expansion (CTE) of the metal layer is constrained by the substrate.

Brief Summary Paragraph Right (24):
A bottom metal layer can be bonded to the insulating substrate opposite the planar surface. This second layer can also be patterned as an electrical circuit. In one embodiment the assembly with such a second layer has cooling elements mounted on the opposite side of the substrate. These cooling elements may include Peltier coolers. Micro-channel coolers using fluid coolants can also be patterned in the second layer of

metal.

2. Document ID: US 6365418 B1

L19: Entry 2 of 26 File: USPT Apr 2, 2002

US-PAT-NO: 6365418
DOCUMENT-IDENTIFIER: US 6365418 B1

TITLE: Arrays of protein-capture agents and methods of use thereof

L19: Entry 2 of 26 File: USPT Apr 2, 2002

US-PAT-NO: 6365418
DOCUMENT-IDENTIFIER: US 6365418 B1

TITLE: Arrays of protein-capture agents and methods of use thereof

DATE-ISSUED: April 2, 2002

US-CL-CURRENT: 436/518; 427/134, 427/2.11, 427/261, 427/287, 427/387, 427/407.2, 427/518, 435/286.1, 435/287.1, 435/287.9, 435/288.3, 435/288.4, 435/7.1, 436/524, 436/525, 436/527, 436/528, 436/532, 436/533, 436/535, 436/536

APPL-NO: 9/ 574748
DATE FILED: May 18, 2000

PARENT-CASE:

This application is a continuation-in-part application of co-pending application Ser. No. 09/115,455, filed, Jul. 14, 1998, which is incorporated herein by reference in its entirety.

L19: Entry 2 of 26 File: USPT Apr 2, 2002

DOCUMENT-IDENTIFIER: US 6365418 B1
TITLE: Arrays of protein-capture agents and methods of use thereof

Detailed Description Paragraph Right (25):
An "organic thinfilm" is a thin layer of organic molecules which has been applied to a substrate or to a coating on a substrate if present. Typically, an organic thinfilm is less than about 20 nm thick. Optionally, an organic thinfilm may be less than about 10 nm thick. An organic thinfilm may be disordered or ordered. For instance, an organic thinfilm can be amorphous (such as a chemisorbed or spin-coated polymer) or highly organized (such as a Langmuir-Blodgett film or self-assembled monolayer). An organic thinfilm may be heterogeneous or homogeneous. Organic thinfilms which are monolayers are preferred. A lipid bilayer or monolayer is a preferred organic thinfilm Optionally, the organic thinfilm may comprise a combination of more than one form of organic thinfilm. For instance, an organic thinfilm may comprise a lipid bilayer on top of a self-assembled monolayer. A hydrogel may also compose an organic thinfilm. The organic thinfilm will typically have functionalities exposed on its surface which serve to enhance the surface conditions of a substrate or the coating on a substrate in any of a number of ways. For instance, exposed functionalities of the organic thinfilm are typically useful in the binding or covalent immobilization of the protein-capture agents to the patches of the array. Alternatively, the organic thinfilm may bear functional groups (such as polyethylene glycol (PEG)) which reduce the non-specific binding of molecules to the surface. Other exposed functionalities serve to tehter the thinfilm to the surface of the substrate or the coating. Particular functionalities of the organic thinfilm may also be designed to enable certain detection techniques to be

used with the surface. Alternatively, the organic thinfilm may serve the purpose of preventing inactivation of a protein-capture agent or the protein to be bound by a protein-capture agent from occurring upon contact with the surface of a substrate or a coating on the surface of a substrate.

Detailed Description Paragraph Right (67):
A variety of techniques may be used to generate patches of organic thinfilm on the surface of the substrate or on the surface of a coating on the substrate. These techniques are well known to those skilled in the art and will vary depending upon the nature of the organic thinfilm, the substrate, and the coating if present. The techniques will also vary depending on the structure of the underlying substrate and the pattern of any coating present on the substrate. For instance, patches of a coating which is highly reactive with an organic thinfilm may have already been produced on the substrate surface. Arrays of patches of organic thinfilm can optionally be created by microfluidics printing, microstamping (U.S. Pat. Nos. 5,512,131 and 5,731,152), or microcontact printing (.mu.CP) (PCT Publication WO 96/29629). Subsequent immobilization of protein-capture agents to the reactive monolayer patches results in two-dimensional arrays of the agents. Inkjet printer heads provide another option for patterning monolayer X-R-Y molecules, or components thereof, or other organic thinfilm components to nanometer or micrometer scale sites on the surface of the substrate or coating (Lemmo et al., Anal Chem., 1997, 69:543-551; U.S. Pat. Nos. 5,843,767 and 5,837,860). In some cases, commercially available arrayers based on capillary dispensing (for instance, OmniGrid.TM. from Genemachines, Inc., San Carlos, Calif., and High-Throughput Microarrayer from Intelligent Bio-Instruments, Cambridge, Mass.) may also be of use in directing components of organic thinfilms to spatially distinct regions of the array.

Detailed Description Paragraph Right (153):
Use of one of the protein-capture agent arrays of the invention may optionally involve placing the two-dimensional array in a flowchamber with approximately 1-10 microliters of fluid volume per 25 mm.sup.2 overall surface area. The cover over the array in the flowchamber is preferably transparent or translucent. In one embodiment, the cover may comprise Pyrex or quartz glass. In other embodiments, the cover may be part of a detection system that monitors interaction between the protein-capture agents immobilized on the array and protein in a solution such as a cellular extract. The flowchambers should remain filled with appropriate aqueous solutions to preserve protein activity. Salt, temperature, and other conditions are preferably kept similar to those of normal physiological conditions. Proteins in a fluid solution may be flushed into the flow chamber as desired and their interaction with the immobilized protein-capture agents determined. Sufficient time must be given to allow for binding between the protein-capture agent and its binding partner to occur. The amount of time required for this will vary depending upon the nature and tightness of the affinity of the protein-capture agent for its binding partner. No specialized microfluidic pumps, valves, or mixing techniques are required for fluid delivery to the array.

Other Reference Publication (3):
Elkins et al. (1991). Multianalyte microspot immunoassay-microanalytical "compact disk" of the future. Clin. Chem. 37(11):1955-1967.*

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

3. Document ID: US 6346387 B1

L19: Entry 3 of 26 File: USPT Feb 12, 2002

US-PAT-NO: 6346387
DOCUMENT-IDENTIFIER: US 6346387 B1

TITLE: Detection of binding reactions using labels detected by mediated catalytic electrochemistry

L19: Entry 3 of 26 File: USPT Feb 12, 2002

US-PAT-NO: 6346387

DOCUMENT-IDENTIFIER: US 6346387 B1

TITLE: Detection of binding reactions using labels detected by mediated catalytic electrochemistry

DATE-ISSUED: February 12, 2002

US-CL-CURRENT: 435/6; 435/91.2, 435/91.5, 435/91.51, 536/23.1, 600/345

APPL-NO: 9/ 722065
DATE FILED: November 24, 2000

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
This is a continuation-in-part of co-pending application Ser. No. 09/603,217, filed Jun. 26, 2000, which is a divisional application of application Ser. No. 09/179,665, filed Oct. 27, 1998, now U.S. Pat. No. 6,132,971, which is a divisional application of application Ser. No. 08/667,338, filed Jun. 20, 1996, now U.S. Pat. No. 5,871,918, which is a continuation-in-part of application Ser. No. 08/495,817, filed Jun. 27, 1995; now abandoned and a continuation-in-part of co-pending application Ser. No. 09/267,552 filed Mar. 12, 1999, now U.S. Pat. No. 6,180,346 which is a continuation-in-part of application Ser. No. 08/667,338, filed Jun. 20, 1996, now U.S. Pat. No. 5,871,918, which is a continuation-in-part of application Ser. No. 08/495,817, filed Jun. 27, 1995; each of which is incorporated herein by reference.

L19: Entry 3 of 26 File: USPT Feb 12, 2002

DOCUMENT-IDENTIFIER: US 6346387 B1
TITLE: Detection of binding reactions using labels detected by mediated catalytic electrochemistry

Brief Summary Paragraph Right (12):
In U.S. Pat. No. 5,968,745 of Thorp et al., a polymer-electrode is provided that is useful for the electrochemical detection of a preselected base in a nucleic acid. The polymer-electrode comprises: (a) a substrate having a conductive working surface; and (b) a polymer layer on the conductive working surface. The polymer layer has a plurality of microfluidic reaction openings distributed throughout the layer. An oligonucleotide probe is preferably bound to the polymer layer.

Brief Summary Paragraph Right (13):
U.S. Pat. No. 6,127,127 provides a self-assembled phosphonate monolayer, which in the preferred embodiment is a carboxy-alkyl phosphonate, on an ITO surface. The oligonucleotide probe is immobilized on an electrode surface modified by the self-assembled monolayer. The electrode with the self-assembled monolayer is useful for the electrochemical detection of a preselected base in a nucleic acid and for determining the presence of a target nucleic acid in a sample, by contacting the self-assembled monolayer with the sample, so that the target nucleic acid and the oligonucleotide probe form a hybridized nucleic acid on the monolayer; reacting the hybridized nucleic acid with a transition metal complex capable of oxidizing a preselected base in the hybridized nucleic acid in an oxidation-reduction reaction; detecting the oxidation-reduction reaction; and determining the presence or absence of the target nucleic acid from the detected oxidation-reduction reaction.

Brief Summary Paragraph Right (14):
In both the polymer-electrode and monolayer patents, determination of the presence of a target protein in a sample can also be achieved and comprises attaching a protein-binding substance to a polymer-electrode or self-assembled monolayer on a conductive working surface according to the invention; exposing the polymer-electrode or monolayer to the sample; exposing the polymer-electrode or monolayer to a second protein-binding substance that has been modified to contain an oligonucleotide label; reacting the polymer-electrode or monolayer with a transition metal complex capable of oxidizing a preselected base in the oligonucleotide label in an oxidation-reduction reaction; detecting the oxidation-reduction reaction; and determining the presence or absence of the target protein from the detected oxidation-reduction reaction. The polymer-electrode or monolayer may be brought into contact with the conductive working surface of the substrate either before or after reacting the polmer-electrode or

monolayer with the first protein binding substance. The target protein may be modified to contain an oligonucleotide label as is known in the art.

Detailed Description Paragraph Right (21):
In order to prepare the electrode for modification with immobilized biological binding entities, the electrode is modified with a suitable nonconductive layer. The nonconductive layer may have one or more of a number of functions including providing covalent attachment of biomolecules, blocking of nonspecific binding to the electrode, and allowing electron transfer between the mediator and the electrode and/or the mediator and the label. The nonconductive layer may be one or more of the following, for example: self-assembled monolayers (e.g., U.S. Pat. No. 6,127,127); cross-linked polymer layers; alkyl silane layers; alkylphosphonate-, alkylphosphate-, carboxyalkane-, alkanethiol-, or alkylamine-based layers; polymer membranes (as in U.S. Pat. No. 5,968,745) and/or one or more layers of biomolecules such as proteins, antibodies, biotin-binding molecules (avidin, streptavidin, neutravidin), protein A, protein G, receptors, or oligonucleotides. In the case of a nonconductive layer comprised of biomolecules, the nonconductive layer can serve as a capture layer for the binder, target protein, the surrogate target, or the affinity ligand. For example, on an electrode designed to detect human chorionic gonadotropin (hCG), the nonconductive layer could be an anti-hCG capture antibody; on an electrode designed to detect a ligand, a receptor molecule could serve as the nonconductive layer. Alternatively, the nonconductive layer can be a biomolecule that binds the capture molecule such as protein A for a capture antibody or an antibody directed against the capture molecule (i.e. an anti-streptavidin antibody for a binding assay using streptavidin as the capture molecule or an anti-receptor antibody for a receptor-based assay). Regardless of the nature of the nonconductive layer, this layer will ultimately be placed in contact with a solution containing the mediator prior to electrochemical detection.

4. Document ID: US 6329209 B1

L19: Entry 4 of 26 File: USPT Dec 11, 2001

US-PAT-NO: 6329209
DOCUMENT-IDENTIFIER: US 6329209 B1

TITLE: Arrays of protein-capture agents and methods of use thereof

L19: Entry 4 of 26 File: USPT Dec 11, 2001

US-PAT-NO: 6329209
DOCUMENT-IDENTIFIER: US 6329209 B1

TITLE: Arrays of protein-capture agents and methods of use thereof

DATE-ISSUED: December 11, 2001

US-CL-CURRENT: 436/518; 427/261, 435/287.9

APPL-NO: 9/ 353555
DATE FILED: July 14, 1999

PARENT-CASE:

This application is a continuation-in-part application of co-pending application Ser. No. 09/115,455, filed Jul. 14, 1998, which is incorporated herein by reference in its entirety.

L19: Entry 4 of 26 File: USPT Dec 11, 2001

DOCUMENT-IDENTIFIER: US 6329209 B1

TITLE: Arrays of protein-capture agents and methods of use thereof

Detailed Description Paragraph Right (25):
An "organic thinfilm" is a thin layer of organic molecules which has been applied to a substrate or to a coating on a substrate if present. Typically, an organic thinfilm is less than about 20 nm thick. Optionally, an organic thinfilm may be less than about 10 nm thick. An organic thinfilm may be disordered or ordered. For instance, an organic thinfilm can be amorphous (such as a chemisorbed or spin-coated polymer) or highly organized (such as a Langmuir-Blodgett film or self-assembled monolayer). An organic thinfilm may be heterogeneous or homogeneous. Organic thinfilms which are monolayers are preferred. A lipid bilayer or monolayer is a preferred organic thinfilm. Optionally, the organic thinfilm may comprise a combination of more than one form of organic thinfilm. For instance, an organic thinfilm may comprise a lipid bilayer on top of a self-assembled monolayer. A hydrogel may also compose an organic thinfilm. The organic thinfilm will typically have functionalities exposed on its surface which serve to enhance the surface conditions of a substrate or the coating on a substrate in any of a number of ways. For instance, exposed functionalities of the organic thinfilm are typically useful in the binding or covalent immobilization of the protein-capture agents to the patches of the array. Alternatively, the organic thinfilm may bear functional groups (such as polyethylene glycol (PEG)) which reduce the non-specific binding of molecules to the surface. Other exposed functionalities serve to tether the thinfilm to the surface of the substrate or the coating. Particular functionalities of the organic thinfilm may also be designed to enable certain detection techniques to be used with the surface. Alternatively, the organic thinfilm may serve the purpose of preventing inactivation of a protein-capture agent or the protein to be bound by a protein-capture agent from occurring upon contact with the surface of a substrate or a coating on the surface of a substrate. Optionally, the organic thinfilm may comprise a combination of more than one form of organic thinfilm. For instance, an organic thinfilm may comprise a lipid bilayer on top of a self-assembled monolayer. A hydrogel may also compose an organic thinfilm. The organic thinfilm will typically have functionalities exposed on its surface which serve to enhance the surface conditions of a substrate or the coating on a substrate in any of a number of ways. For instance, exposed functionalities of the organic thinfilm are typically useful in the binding or covalent immobilization of the protein-capture agents to the patches of the array. Alternatively, the organic thinfilm may bear functional groups (such as polyethylene glycol (PEG)) which reduce the non-specific binding of molecules to the surface. Other exposed functionalities serve to tehter the thinfilm to the surface of the substrate or the coating. Particular functionalities of the organic thinfilm may also be designed to enable certain detection techniques to be used with the surface. Alternatively, the organic thinfilm may serve the purpose of preventing inactivation of a protein-capture agent or the protein to be bound by a protein-capture agent from occurring upon contact with the surface of a substrate or a coating on the surface of a substrate.

Detailed Description Paragraph Right (67):
A variety of techniques may be used to generate patches of organic thinfilm on the surface of the substrate or on the surface of a coating on the substrate. These techniques are well known to those skilled in the art and will vary depending upon the nature of the organic thinfilm, the substrate, and the coating if present. The techniques will also vary depending on the structure of the underlying substrate and the pattern of any coating present on the substrate. For instance, patches of a coating which is highly reactive with an organic thinfilm may have already been produced on the substrate surface. Arrays of patches of organic thinfilm can optionally be created by microfluidics printing, microstamping (U.S. Pat. Nos. 5,512,131 and 5,731,152), or microcontact printing (.mu.CP) (PCT Publication WO 96/29629). Subsequent immobilization of protein-capture agents to the reactive monolayer patches results in two-dimensional arrays of the agents. Inkjet printer heads provide another option for patterning monolayer X-R-Y molecules, or components thereof, or other organic thinfilm components to nanometer or micrometer scale sites on the surface of the substrate or coating (Lemmo et al., Anal Chem., 1997, 69:543-551; U.S. Pat. Nos. 5,843,767 and 5,837,860). In some cases, commercially available arrayers based on capillary dispensing (for instance, OmniGrid.TM. from Genemachines, inc, San Carlos, Calif., and High-Throughput Microarrayer from Intelligent Bio-Instruments, Cambridge, Mass.) may also be of use in directing components of organic thinfilms to spatially distinct regions of the array.

Detailed Description Paragraph Right (153):
Use of one of the protein-capture agent arrays of the invention may optionally involve placing the two-dimensional array in a flowchamber with approximately 1-10 microliters of fluid volume per 25 mm.sup.2 overall surface area. The cover over the array in the

flowchamber is preferably transparent or translucent. In one embodiment, the cover may comprise Pyrex or quartz glass. In other embodiments, the cover may be part of a detection system that monitors interaction between the protein-capture agents immobilized on the array and protein in a solution such as a cellular extract. The flowchambers should remain filled with appropriate aqueous solutions to preserve protein activity. Salt, temperature, and other conditions are preferably kept similar to those of normal physiological conditions. Proteins in a fluid solution may be flushed into the flow chamber as desired and their interaction with the immobilized protein-capture agents determined. Sufficient time must be given to allow for binding between the protein-capture agent and its binding partner to occur. The amount of time required for this will vary depending upon the nature and tightness of the affinity of the protein-capture agent for its binding partner. No specialized microfluidic pumps, valves, or mixing techniques are required for fluid delivery to the array.

Other Reference Publication (8):
Elkins et al. (1991). Multianalyte microspot immunoassay-microanalytical "compact disk" of the future. Clin. Chem. 37(11):1955-1967.*

5. Document ID: US 6322979 B1

L19: Entry 5 of 26 File: USPT Nov 27, 2001

US-PAT-NO: 6322979
DOCUMENT-IDENTIFIER: US 6322979 B1

TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

L19: Entry 5 of 26 File: USPT Nov 27, 2001

US-PAT-NO: 6322979
DOCUMENT-IDENTIFIER: US 6322979 B1

TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

DATE-ISSUED: November 27, 2001

US-CL-CURRENT: 435/6; 536/24.3

APPL-NO: 9/ 296078
DATE FILED: April 21, 1999

PARENT-CASE:

RELATED APPLICATIONS
This is a divisional of application Ser. No. 08/786,187 filed Jan. 21. 1997. now allowed, which is a continuation-in-part, of U.S. patent application Ser. No. 08/312,388, filed Sep. 26, 1994 by Bamdad, et al., now U.S. Pat. No. 5,620,850.

L19: Entry 5 of 26 File: USPT Nov 27, 2001

DOCUMENT-IDENTIFIER: US 6322979 B1
TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

Brief Summary Paragraph Right (38):
The present invention provides yet another method of capturing a biological molecule. This method involves providing a solid phase that has a surface having adhered thereto a species having a formula X--R--Ch--M--BP, in which X represents a functional group that adheres to the surface, R represents a self-assembled monolayer-promoting spacer moiety, Ch represents a chelating agent that coordinates a metal ion, M represents a

metal ion coordinated by the chelating agent, and BP represents a binding partner of the biological molecule, coordinated to the metal ion. A target molecule then is allowed to biologically bind to the binding partner. The biological molecule then can be determined, for example by detecting a physical change associated with the surface An article provided in accordance with the invention can be a biosensor element, such as a SPR chip, and the determination carried out by measuring surface plasmon resonance associated with the chip. The methods of the invention that involve capturing a molecule can involve removal of a preselected molecule, such as a biological molecule, from a fluid medium.

Detailed Description Paragraph Right (43):
The articles of the present invention can be used for a variety of applications, including biosensing applications, test assays, and the like. The term "test assay" generally refers to any procedure in which a member of a biological binding partner pair is to be captured from a medium in which it is dispersed. For example, "test assay" may be used to describe a diagnostic procedure, analytical procedure, microanalytical procedure, forensic analysis, pharmacokinetic study, cell sorting procedure, affinity chromatogram, industrial or laboratory recovery or analysis of one or more species such as toxins, catalysts, or starting materials or products, and the like. a typical test assay is an immunoassay. Biosensing applications include those such as drug screening, environmental monitoring, medical diagnostics, quality control in the pharmaceutical and food industries, and other areas in which it is advantageous to sensitively determine biological binding between partners.

6. Document ID: US 6322963 B1

L19: Entry 6 of 26 File: USPT Nov 27, 2001

US-PAT-NO: 6322963
DOCUMENT-IDENTIFIER: US 6322963 B1

TITLE: Sensor for analyte detection

L19: Entry 6 of 26 File: USPT Nov 27, 2001

US-PAT-NO: 6322963
DOCUMENT-IDENTIFIER: US 6322963 B1

TITLE: Sensor for analyte detection

DATE-ISSUED: November 27, 2001

US-CL-CURRENT: 435/4; 204/164, 204/193, 204/403.01, 204/403.04, 204/403.14, 205/372, 205/777.5, 205/81, 422/50, 422/82.01, 435/283.1, 435/287.1, 435/289.1, 435/817

APPL-NO: 9/ 701906
DATE FILED: December 5, 2000

PARENT-CASE:

This Application is a 371 of PCT/IL99/00309 filed Jun. 10, 1999, which is a CIP of Ser. No. 09/110,686 filed Jul. 7, 1998 as U.S. Pat. No. 6,096,497.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
IL	124903	June 15, 1998
IL	125720	August 19, 1998
IL	127019	November 12, 1998
IL	129754	May 4, 1999

PCT-DATA:					
APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/IL99/00309	June 10, 1999	WO99/66322	Dec 23, 1999	Dec 5, 2000	Dec 5, 2000

L19: Entry 6 of 26 File: USPT Nov 27, 2001

DOCUMENT-IDENTIFIER: US 6322963 B1
TITLE: Sensor for analyte detection

Brief Summary Paragraph Right (25):
The invention provides a method for detecting an analyte, having the following steps: providing an electrically conductive base member; immobilizing at least one macromolecule in proximity to the base member, wherein the macromolecule is capable of interacting at a level of specificity with a predetermined analyte; exposing analyte to the macromolecule; and detecting an electrical signal induced in or about the base member, wherein the detected electrical signal is responsive to analyte presence or interaction with the macromolecule. Optionally a self-assembled monolayer is bound to the base member, the macromolecules are immobilized proximate to the self-assembled monolayer.

Detailed Description Paragraph Right (2):
A typical sensor comprises (i) a multilayer substrate comprising a conducting base member or layer and an optional self-assembled monolayer (or other chemical entity that rests between the base member and the macromolecules); (ii) at least one macromolecule that displays a level of affinity of interaction toward a predetermined analyte or group of analytes; and (iii) a detection unit for measuring an electromotive force (emf), current or other electrical feature electromagnetically induced in or about the base member and responsive to the presence of analyte.

Detailed Description Paragraph Right (77):
Human receptor molecules are immobilized along the electrically-conductive lanes of a highly-parallel microfluidic analytic chip. The receptors are the macromolecular entities, while the lanes serve as multiple base members. Chemical products of a combinatorial library are sequentially exposed to the immobilized macromolecules (receptor), and a computer (880 in FIG. 8) monitors for interaction between the chemicals and the receptor molecules. Interactions that lead to altered induced emf readings (relative to background in absence of chemicals) in one or more base member units (820-823 in FIG. 8) are noted, and the corresponding chemicals are selected as lead compounds in the synthesis of ligands for this target receptor. A 200-lane system that allows for ninety seconds of interaction for each chemical with macromolecules allows for screening of 192,000 chemicals per twenty-four hours.

7. Document ID: US 6306584 B1

L19: Entry 7 of 26 File: USPT Oct 23, 2001

US-PAT-NO: 6306584
DOCUMENT-IDENTIFIER: US 6306584 B1

TITLE: Electronic-property probing of biological molecules at surfaces

L19: Entry 7 of 26 File: USPT Oct 23, 2001

US-PAT-NO: 6306584
DOCUMENT-IDENTIFIER: US 6306584 B1

TITLE: Electronic-property probing of biological molecules at surfaces

DATE-ISSUED: October 23, 2001

US-CL-CURRENT: 435/6; 435/7.1, 536/24.3, 536/26.6

APPL-NO: 8/ 843623
DATE FILED: April 10, 1997

PARENT-CASE:

RELATED APPLICATION
This application is a continuation-in-part of U.S. application Ser. No. 08/804,883 by Cynthia C. Bamdad entitled "Electronic-Property Probing of Biological Molecules at Surfaces", filed Feb. 24, 1997, now abandoned, which is a continuation-in part of U.S. application Ser. No. 08/786,153 by Cynthia C. Bamdad entitled "Surface-Immobilized Nucleic Acid and Electron-Transfer Devices and Methods Employing the Same", filed Jan. 21, 1997, now abandoned.

DOCUMENT-IDENTIFIER: US 6306584 B1
TITLE: Electronic-property probing of biological molecules at surfaces

Abstract Paragraph Left (1):
A technique for immobilizing biological molecules, in particular nucleic acid strands, is described. Biological molecules immobilized at surfaces can be used in electron-transfer detection techniques in which a binding partner of a biological molecule is brought into proximity of the surface-immobilized biological molecule, an electrical potential created between the two biologically-binding species, and electron transfer through the species determined. Another technique involves immobilizing a bioligical molecule such as a protein, DNA, etc. at a surface via a self-assembled monolayer, affecting the biological molecule via, for example, biological binding, inducing a change in conformation via a prion, etc., and detecting an electronic property change in the molecule via a change in inpedence associated with an electronic circuit addressed by the biological molecule. These technique facilitates combinatorial array detection articles.

Brief Summary Paragraph Right (1):
The present invention relates generally to the derivatization of surfaces for determination of analytes, for example from a fluid medium using a biological binding partner of an analyte, and more particularly to the formation, on a surface, of a self-assembled molecular monolayer including a biological species such as a nucleic acid strand, and the use of the self-assembled monolayer in a probe that acts to detect molecular recognition via electronic properties of the biological species.

Brief Summary Paragraph Right (17):
The present invention provides yet another method of capturing a biological molecule. This method involves providing a solid phase that has a surface having adhered thereto a species having a formula X--R--Ch--M--BP, in which X represents a functional group that adheres to the surface, R represents a self-assembled monolayer-promoting spacer moiety, Ch represents a chelating agent that coordinates a metal ion, M represents a metal ion coordinated by the chelating agent, and BP represents a binding partner of the biological molecule, coordinated to the metal ion. A target molecule then is allowed to biologically bind to the binding partner. The biological molecule then can be determined, for example by detecting a physical change associated with the surface.

Detailed Description Paragraph Right (58):
The articles of the present invention can be used for a variety of applications, including biosensing applications, test assays, and the like. The term "test assay" generally refers to any procedure in which a member of a biological binding partner pair is to be captured from a medium in which it is dispersed. For example, "test assay" may be used to describe a diagnostic procedure, analytical procedure, microanalytical procedure, forensic analysis, pharmacokinetic study, cell sorting procedure, affinity chromatogram, industrial or laboratory recovery or analysis of one or more species such as toxins, catalysts, or starting materials or products, and the like. a typical test assay is an immunoassay. Biosensing applications include those such as drug screening, environmental monitoring, medical diagnostics, quality control

in the pharmaceutical and food industries, and other areas in which it is advantageous to sensitively determine biological binding between partners.

Detailed Description Paragraph Right (61):
The embodiment of the invention that involves a SAM-forming species including a nucleic acid strand (or multiple nucleic acid strands) can be used: 1) to detect DNA hybridization (human genome project, diagnostic scanning of DNA for genetic mutants), 2) to present DNA-binding proteins for the study of subsequent protein-protein interactions for which DNA binding is a critical element of the interaction, using instruments such as SPR devices, 3) to build an easy analysis DNA computer. Additionally, both the species X--R--Ch and the species X--R--NA can be used in ultra high through put devices to detect interactions by monitoring the time dependence of electron transfer from bait to prey. The biospecific species self-assemble on a surface such as a metal surface, such as a gold-coated electrode. A peptide or DNA library is generated such that it is also attached to a metal. Specifically, a mixed self-assembled monolayer can be first formed on a gold substrate. The major component is an inert tri-ethylene glycol terminated thiol and the minor component terminates in a photolabile group. Using previously-described masking techniques, a DNA or peptide library is generated such that the spatial address of each species is known. The surfaces are brought into close proximity (atomic force microscopy; AFM technology) so that electrons generating from the goldtipped electrode travel through a known species immobilized on the electrode via, for example, SAM formation, to a second metal surface, through the surface immobilized library components (peptides or DNA) if and only if there is biological binding between the two. The transfer of electrons from the electrode through individual components of the library can be monitored by a detection array beneath the metal of the library support. Alternatively, a direct interaction can be gleaned from the time dependence of conductance returning to the electrode when an alternating current is applied. The minor component of the self-assembled monolayers can be phenyleneethynylene thiolates in this embodiment since it has been shown that they have higher conductance than alkanethiolates. However, the two thiols when mixed will form an ordered SAM (See, e.g., Science, "Are Single Molecular Wires Conducting?", Vol. 271, 1996, pgs. 1705-1707).

8. Document ID: US 6291889 B1

L19: Entry 8 of 26 File: USPT Sep 18, 2001

US-PAT-NO: 6291889
DOCUMENT-IDENTIFIER: US 6291889 B1

TITLE: High temperature resistant thin-film system

L19: Entry 8 of 26 File: USPT Sep 18, 2001

US-PAT-NO: 6291889
DOCUMENT-IDENTIFIER: US 6291889 B1

TITLE: High temperature resistant thin-film system

DATE-ISSUED: September 18, 2001

US-CL-CURRENT: 257/763; 257/764

APPL-NO: 9/ 167815
DATE FILED: October 7, 1998

PARENT-CASE:

This application is a divisional of Ser. No. 08/421,809, filed Apr. 12, 1995, now Pat. No. 5,856,235.

L19: Entry 8 of 26 File: USPT Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6291889 B1
TITLE: High temperature resistant thin-film system

Brief Summary Paragraph Right (6):
To maintain an interconnect directly behind each pixel in the Z direction the module layers must be kept very thin, usually less than one pixel center-to-center spacing. The layers, which are ceramic substrates having thin-film microcircuits printed thereupon, are laminated using extremely thin thermal setting adhesive sheets. A principal shortcoming to this laminated multi-layer assembly is the poor dimension stability that exists due to a mismatch of the coefficients of expansion between the ceramic layers and the thermal set adhesive sheets. To alleviate this problem in the past, a thermal-stress barrier commonly known as a buffer board, was used to absorb the thermal stress from the module. The buffer board was placed between the infrared detector arrays and the module and thus provides for electrical and mechanical interconnection therebetween.

Brief Summary Paragraph Right (10):
More specifically, in the Z-technology ceramic multi-chip modules, thin-film materials are sputter deposited onto thin-film grade alumina (99.6% Al.sub.2 O.sub.3) substrates and delineated to form the required microchip patterns. Sputtering is a process in which material is removed from a source (the cathode) and accelerated through a plasma and deposited on the substrate (the anode). Then individual pattern layers are laminated together to form a multi-layer Z-module using a glass fusion-lamination technique, as described in Hornback, U.S. Pat. No. 5,128,749. The fusion-lamination process uses low temperature firable glass at temperatures as high as 600.degree. C. with pressure up to 300 kN/m.sup.2. Under these conditions, however, microcircuits made with sputtered thin-film materials have failed on the conventional substrates due to the factors described above.

9. Document ID: US 6290839 B1

L19: Entry 9 of 26 File: USPT Sep 18, 2001

US-PAT-NO: 6290839
DOCUMENT-IDENTIFIER: US 6290839 B1

TITLE: Systems for electrophoretic transport and detection of analytes

L19: Entry 9 of 26 File: USPT Sep 18, 2001

US-PAT-NO: 6290839
DOCUMENT-IDENTIFIER: US 6290839 B1

TITLE: Systems for electrophoretic transport and detection of analytes

DATE-ISSUED: September 18, 2001

US-CL-CURRENT: 205/777.5; 204/403.14, 204/409, 204/450, 204/452, 204/600, 204/603

APPL-NO: 9/ 134058
DATE FILED: August 14, 1998

PARENT-CASE:

This application claims the benefit of U.S. Provisional Application No. 60/090,389, filed Jun. 23, 1998.

L19: Entry 9 of 26 File: USPT Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6290839 B1
TITLE: Systems for electrophoretic transport and detection of analytes

Abstract Paragraph Left (1):
The invention relates to compositions and methods useful in the electrophoretic transport of target analytes to a detection electrode comprising a self-assembled monolayer (SAM). Detection proceeds through the use of an electron transfer moiety (ETM) that is associated with the target analyte, either directly or indirectly, to allow electronic detection of the ETM.

Brief Summary Paragraph Right (1):
The invention relates to compositions and methods useful in the electrophoretic transport of target analytes to a detection electrode comprising a self-assembled monolayer (SAM). Detection proceeds through the use of an electron transfer moiety (ETM) that is associated with the target analyte, either directly or indirectly, to allow electronic detection of the ETM.

Brief Summary Paragraph Right (4):
The use of electrophoresis in microfluidic methods to facilitate the binding of biological molecules to their binding partners for subsequent detection is known; see for example U.S. Patent Nos. 5,605,662 and 5,632,957, and references disclosed therein.

Detailed Description Paragraph Right (31):
The detection electrode comprises a self-assembled monolayer (SAM) comprising conductive oligomers. By "monolayer" or "self-assembled monolayer" or "SAM" herein is meant a relatively ordered assembly of molecules spontaneously chemisorbed on a surface, in which the molecules are oriented approximately parallel to each other and roughly perpendicular to the surface. Each of the molecules includes a functional group that adheres to the surface, and a portion that interacts with neighboring molecules in the monolayer to form the relatively ordered array. A "mixed" monolayer comprises a heterogeneous monolayer, that is, where at least two different molecules make up the monolayer. The SAM may comprise conductive oligomers alone, or a mixture of conductive oligomers and insulators. As outlined herein, the efficiency of target analyte binding (for example, oligonucleotide hybridization) may increase when the analyte is at a distance from the electrode. Similarly, non-specific binding of biomolecules, including the target analytes, to an electrode is generally reduced when a monolayer is present. Thus, a monolayer facilitates the maintenance of the analyte away from the electrode surface. In addition, a monolayer serves to keep charged species away from the surface of the electrode. Thus, this layer helps to prevent electrical contact between the electrodes and the ETMs, or between the electrode and charged species within the solvent. Such contact can result in a direct "short circuit" or an indirect short circuit via charged species which may be present in the sample. Accordingly, the monolayer is preferably tightly packed in a uniform layer on the electrode surface, such that a minimum of "holes" exist. The monolayer thus serves as a physical barrier to block solvent accesibility to the electrode.

Other Reference Publication (94):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

CLAIMS:

1. A method of detecting a target analyte in a sample comprising:

a) placing said sample in an electric field between at least a first electrode and at least a second electrode sufficient to cause electrophoretic transport of said sample to the vicinity of a detection electrode comprising a self-assembled monolayer, wherein said target analyte directly or indirectly comprises at least one electron transfer moiety (ETM);

b) detecting the presence of said ETM using said detection electrode.

9. A method of detecting a target nucleic acid sequence in a sample comprising:

a) placing said sample in an electric field between at least a first electrode and at

least a second electrode sufficient to cause electrophoretic transport of said sample to the vicinity of a detection electrode comprising a self-assembled monolayer, wherein said target sequence directly or indirectly comprises at least one electron transfer moiety (ETM);

b) detecting the presence of said ETM using said detection electrode.

27. A method of detecting a target analyte in a sample comprising:

a) placing said sample in an electric field between at least a first electrode and at least a second electrode sufficient to cause electrophoretic transport of said sample to the vicinity of a detection electrode comprising a self-assembled monolayer, wherein said target analyte directly comprises at least one electron transfer moiety (ETM);

b) detecting the presence of said ETM using said detection electrode.

28. A method of detecting a target nucleic acid sequence in a sample comprising:

a) placing said sample in an electric field between at least a first electrode and at least a second electrode sufficient to cause electrophoretic transport of said sample to the vicinity of a detection electrode comprising a self-assembled monolayer, wherein said target sequence directly comprises at least one electron transfer moiety (ETM);

b) detecting the presence of said ETM using said detection electrode.

10. Document ID: US 6284197 B1

L19: Entry 10 of 26 File: USPT Sep 4, 2001

US-PAT-NO: 6284197
DOCUMENT-IDENTIFIER: US 6284197 B1

TITLE: Optical amplification of molecular interactions using liquid crystals

L19: Entry 10 of 26 File: USPT Sep 4, 2001

US-PAT-NO: 6284197
DOCUMENT-IDENTIFIER: US 6284197 B1

TITLE: Optical amplification of molecular interactions using liquid crystals

DATE-ISSUED: September 4, 2001

US-CL-CURRENT: 422/82.05; 422/55, 422/57, 422/68.1, 422/82.01, 435/4, 435/6, 435/7.1, 435/7.4, 435/7.5, 436/4, 436/501, 436/524, 436/528, 436/805

APPL-NO: 9/ 127382
DATE FILED: July 31, 1998

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
This application is a continuation of and claims the benefit of U.S. application Ser. No. 09/092,453, filed Jun. 5, 1998, now abandoned, the disclosure of which is incorporated by reference.

L19: Entry 10 of 26 File: USPT Sep 4, 2001

DOCUMENT-IDENTIFIER: US 6284197 B1
TITLE: Optical amplification of molecular interactions using liquid crystals

Abstract Paragraph Left (1):
Interactions between molecules which are components of self-assembled monolayers and other molecules can be amplified and transduced into an optical signal through the use of a mesogenic layer. The invention provides a device and methods for detecting analytes. The device comprises a substrate onto which a self-assembled monolayer is attached and a mesogenic layer which is anchored by the self-assembled monolayer. The mesogenic layer undergoes a change in conformation in response to the molecular interaction.

Brief Summary Paragraph Right (13):
Liquid crystal devices which undergo anchoring transitions as a result of protein-ligand binding have been reported by Gupta, V. K., Abbott, N. L., Science 276:1533-1536 (1998). Switchable liquid crystals supported on self-assembled monolayers were used to detect the binding of avidin and goat-anti-biotin to a biotinylated self-assembled monolayer. Biotin exhibits a very specific, high affinity binding to both avidin (Kd.about.10.sup.-15) and anti-biotin (Kd.about.10.sup.-9). Gupta et al. teaches the binding of biotin to the self-assembled monolayer and the interaction of this ligand with proteins which are known to display specific and strong binding to biotin.

Detailed Description Paragraph Right (223):
Surfaces were designed with nanometer-scale topographies that could be erased by the specific binding of a protein to surface-immobilized ligands (FIG. 1A), thus leading to macroscopic changes in the orientations of liquid crystals supported on these surfaces. First, thin fins of polycrystalline gold were prepared (FIG. 1B) with roughnesses characterized by a maximum amplitude of .apprxeq.2 nm and a maximum wavelength of .apprxeq.50 nm (FIG. 1C). The deposition of the gold films was controlled so as to introduce an anisotropic roughness within the films (called hereafter "anisotropic gold films (V. K. Gupta et al., Langmuir 12, 2587 (1996)). Although subtle, the anisotropic roughness was easily detected by observing the orientations of supported liquid crystals (V. K. Gupta et al., Langmuir 12, 2587 (1996)). Second, mixed, self-assembled monolayers (SAMs) were formed from Biotin-(CH.sub.2).sub.2 [(CH.sub.2).sub.2 O].sub.2 NHCO(CH.sub.2).sub.11 SH (BiSH) (J. Spinke et al., J. Chem. Phys. 99, 7012 (1993)) and CH.sub.3 (CH.sub.2).sub.7 SH (C.sub.8 SH) by immersion of the films of anisotropic gold in ethanolic solutions containing 9.6 .mu.M of BiSH and 70.4 .mu.M of C.sub.8 SH for 8 hours (Mixed SAMs were also formed in a few minutes by using solutions that contained millimolar concentrations of the organothiols). The mixed SAMs were estimated to consist of 27% biotinylated species by linear interpolation of thicknesses (.DELTA.) of single component SAMs formed from BiSH (.DELTA..sub.BiSH =3.8 nm) and C.sub.8 SH (.DELTA..sub.C8SH =1 nm) (All thickness measurements were performed using a Rudolph Auto ellipsometer with light (633 nm) incident at an angle of 70.degree.. A refractive index of 1.45 was used to estimate the thickness of bound layers of thiols and proteins. Standard deviations of ellipsometric thicknesses (.DELTA.) reported in this paper are +/-0.2 nm). Binding of the protein avidin (Av, 4.2 nm.times.4.2 nm.times.5.6 nm) (P. C. Weber et al., Science, 243, 85 (1989)) to biotin hosted within these SAMs was achieved by incubating the SAMs for 10-15 minutes in phosphate-buffered saline (PBS) (pH 7.4, 100 mM NaCl, 0.004% by volume Triton X-100) containing 0.5 .mu.M of Av (K. L. Prime et al., J. Am. Chem. Soc. 115, 10714 (1993)). The surfaces were then rinsed in deionized water for .about.30 seconds and dried with a stream of nitrogen for .about.30 seconds. To form liquid crystal cells, two SAMs were spaced apart using thin plastic film Mylar.TM. or Saranwrap.TM.) and then secured using paper clips (FIG. 2). Using capillarity, a drop of 4-cyano-4'-pentylbiphenyl (5CB) was drawn in its isotropic phase (isotropic-nematic transition .about.34.degree. C.) into the cavity formed by the two surfaces. The liquid crystal was then cooled towards room temperature: a nematic texture was observed to spread across a 1 cm.times.1 cm-sized cell in .about.5-10 seconds. Optical images of the cell were recorded on a polarization microscope using transmission mode.

Other Reference Publication (24):
Kumar, A., et al., "Patterned Self-Assembled Monolayers and Meso-Scale Phenomena," Acc. Chem. Res., 28:219-226 (1995).

CLAIMS:

1. A method of visually detecting an analyte-recognition moiety complex formed by an interaction between an analyte and a recognition moiety for said analyte by transducing said interaction to an organic mesogenic layer, said method comprising:

(a) interacting said analyte with a surface comprising said recognition moiety, thereby forming an analyte-recognition moiety complex, said surface comprising:

(i) a substrate;

(ii) a self-assembled organosulfur or oganosilane monolayer bound to substrate; and

(iii) said recognition moiety bound to said self-assembled monolayer;

(b) contacting said analyte-recognition moiety complex with said organic mesogenic layer, thereby anchoring said organic mesogenic layer onto said self-assembled monolayer and causing at least a portion of a plurality of mesogens proximate to said recognition moiety to detectably switch from a first orientation to a second orientation, thereby transducing said interaction to said mesogenic layer, said transducing causing said mesogenic layer to register a visually detectable feature; and

(c) visually detecting said feature.

11. Document ID: US 6264825 B1

L19: Entry 11 of 26 File: USPT Jul 24, 2001

US-PAT-NO: 6264825
DOCUMENT-IDENTIFIER: US 6264825 B1

TITLE: Binding acceleration techniques for the detection of analytes

L19: Entry 11 of 26 File: USPT Jul 24, 2001

US-PAT-NO: 6264825
DOCUMENT-IDENTIFIER: US 6264825 B1

TITLE: Binding acceleration techniques for the detection of analytes

DATE-ISSUED: July 24, 2001

US-CL-CURRENT: 205/777.5; 204/403.01, 204/409, 204/450, 204/452, 204/600, 204/603

APPL-NO: 9/ 338726
DATE FILED: June 23, 1999

PARENT-CASE:

This application is a continuing application of U.S. Ser. No. 09/134,058, filed Aug. 14, 1998 and claims the benefit of U.S. Provisional Application Ser. No. 60/090,389, filed Jun. 23, 1998.

L19: Entry 11 of 26 File: USPT Jul 24, 2001

DOCUMENT-IDENTIFIER: US 6264825 B1
TITLE: Binding acceleration techniques for the detection of analytes

Brief Summary Paragraph Right (4):
The use of electrophoresis in microfluidic methods to facilitate the binding of biological molecules to their binding partners for subsequent detection is known; see

for example U.S. Pat. Nos. 5,605,662 and 5,632,957, and references disclosed therein.

Detailed Description Paragraph Right (92):
The detection electrode comprises a self-assembled monolayer (SAM). By "monolayer" or "self-assembled monolayer" or "SAM" herein is meant a relatively ordered assembly of molecules spontaneously chemisorbed on a surface, in which the molecules have a preferred orientation relative to each other (e.g. are oriented approximately parallel to each other) and a preferred orientation relative to the surface (e.g. roughly perpendicular to it). Each of the molecules includes a functional group that adheres to the surface, and a portion that interacts with neighboring molecules in the monolayer to form the relatively ordered array. A "mixed" monolayer comprises a heterogeneous monolayer, that is, where at least two different molecules make up the monolayer. The SAM may comprise conductive oligomers alone, or a mixture of conductive oligomers and insulators. As outlined herein, the efficiency of target analyte binding (for example, oligonucleotide hybridization) may increase when the analyte is at a distance from the electrode. Similarly, non-specific binding of biomolecules, including the target analytes, to an electrode is generally reduced when a monolayer is present. Thus, a monolayer facilitates the maintenance of the analyte away from the electrode surface. In addition, a monolayer serves to keep extraneous electroactive species away from the surface of the electrode. Thus, this layer helps to prevent electrical contact between the electrodes and the ETMs, or between the electrode and extraneous electroactive species within the solvent. Such contact can result in a direct "short circuit" or an indirect short circuit via charged species which may be present in the sample. Accordingly, in one embodiment, the monolayer is preferably tightly packed in a uniform layer on the electrode surface, such that a minimum of "holes" exist. In this embodiment, the monolayer thus serves as a physical barrier to block solvent accesibility to the electrode.

Other Reference Publication (80):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

CLAIMS:

1. A method of detecting a target analyte in a sample comprising:

a) concentrating said target analyte in a detection chamber comprising a detection electrode comprising a self-assembled monolayer and a covalently attached capture ligand;

b) binding said target analyte to said capture ligand to form an assay complex, wherein said assay complex further comprises at least one electron transfer moiety (ETM); and

c) detecting the presence of said ETM using said detection electrode.

13. A method of detecting a target analyte in a sample comprising:

a) flowing said sample past a detection electrode comprising a self-assembled monolayer and a covalently attached capture ligand under conditions that result in the formation of an assay complex comprising said target analyte and said capture ligand, wherein said assay complex further comprises at least one electron transfer moiety (ETM); and

c) detecting the presence of said ETM using said detection electrode.

17. A method of detecting a target nucleic acid sequence in a sample comprising:

a) indirectly or directly hybridizing said target sequence to a capture probe covalently attached to a detection electrode comprising a self-assembled monolayer to form an assay complex, wherein said assay complex is formed in the presence of a hybridization accelerator, wherein said assay complex further comprises at least one electron transfer moiety (ETM); and

b) detecting the presence of said ETM using said detection electrode.

12. Document ID: US 6246330 B1

L19: Entry 12 of 26 File: USPT Jun 12, 2001

US-PAT-NO: 6246330
DOCUMENT-IDENTIFIER: US 6246330 B1

TITLE: Elimination-absorber monitoring system

L19: Entry 12 of 26 File: USPT Jun 12, 2001

US-PAT-NO: 6246330
DOCUMENT-IDENTIFIER: US 6246330 B1

TITLE: Elimination-absorber monitoring system

DATE-ISSUED: June 12, 2001

US-CL-CURRENT: 340/604; 340/384.1, 340/391.1, 340/573.1, 340/605, 604/361

APPL-NO: 9/ 087782
DATE FILED: May 29, 1998

L19: Entry 12 of 26 File: USPT Jun 12, 2001

DOCUMENT-IDENTIFIER: US 6246330 B1
TITLE: Elimination-absorber monitoring system

Detailed Description Paragraph Right (35):
As illustrated in FIG. 1, FIG. 3, FIG. 3A, and FIG. 16, layer 400 also has a series of elongated openings 410, preferably shaped like and disposed directly above and in communication with elongated openings 252, 330, and 352. These aligned openings offer direct conduits to the upper surfaces of electrically conductive members 202 and 204 for feces-specific detection purposes. In one embodiment, openings 410 are slightly narrower than openings 252, 330 and 352, or can be merely slits pre-cut through the material of layer 400 in order to provide additional protection against either urine-splash entrance, or direct contact between conductive layer 200 and the skin. The material of layer 400 is preferably sufficiently thin and flexible for openings 410 to be readily moved apart by the presence of feces, thus facilitating the efficient collection and intrusion of such material first through layer 400, and then through aligned openings 352, 330 and 252 and therethrough directly into contact with layer 200 upon elimination. In various embodiments, slits 410 can be adapted into flaps that remain nominally closed when feces are not present. In still other embodiments, somewhat wider openings can be used, or a series of small, possibly non-elongated openings of any shape could serve the function described. Regardless of the number, shape, or width of openings 410, each such opening must have at least one areal dimension sufficiently narrow with respect to (e.g., very roughly equal to) the overall depth of the aligned series of openings beneath it (as is determined by measurement of the minimum compressible assembled thickness of layers 400, 350 and 250). Such aspect ratio of the aligned openings effectively eliminates the possibility of a diaper wearer's skin ever being pressed into openings 410 deeply enough to touch members 202 and 204, and thereby compromise sensor performance--although such occurrence would not, in any case, be harmful to the wearer.

Detailed Description Paragraph Right (93):
As examples of alternative embodiments of monitor circuit 900, FIG. 24A, FIG. 24B, FIG. 24C and FIG. 24D show four variations of alternative programmable microcontroller-based embodiments. As is well known by those involved with the electronics industry, several families of "low-end" CMOS microcontroller chips (such as a Microchip Technology PIC12CXX device shown in these diagrams), having various attractive specifications and

capabilities, are available from a number of manufacturers at relatively low cost. The use of a microcontroller chip, instead of the discrete logic of FIG. 23, offers the advantage of lower component-count on the monitor unit's circuit board and as a result, also likely lower assembly cost. A microcontroller-based embodiment may also minimize the range of observed variations in the time-based functions of the monitor system from unit to unit, by reducing the number of separate resistor/capacitor time-constant combinations needed, although this is not really a critical issue, given the low timing precision required (probably no better than about +/-10%, in general). Another possible advantage would be the relative ease of changing timing values or other aspects of the monitor system's operation, if desired, by revising the firmware programmed into the microcontroller chip--instead of by changing component values or other hardware. Also, the different functions can easily have separate timing constants without incurring the overhead of additional hardware (such as durations used for sensor-pulsing vs. alarm indication, or audible vs. visual alarm indication).

13. Document ID: US 6221579 B1

L19: Entry 13 of 26 File: USPT Apr 24, 2001

US-PAT-NO: 6221579
DOCUMENT-IDENTIFIER: US 6221579 B1

TITLE: Patterned binding of functionalized microspheres for optical diffraction-based biosensors

L19: Entry 13 of 26 File: USPT Apr 24, 2001

US-PAT-NO: 6221579
DOCUMENT-IDENTIFIER: US 6221579 B1

TITLE: Patterned binding of functionalized microspheres for optical diffraction-based biosensors

DATE-ISSUED: April 24, 2001

US-CL-CURRENT: 435/5; 435/287.2, 435/287.9, 435/7.21

APPL-NO: 9/ 210016
DATE FILED: December 11, 1998

L19: Entry 13 of 26 File: USPT Apr 24, 2001

DOCUMENT-IDENTIFIER: US 6221579 B1
TITLE: Patterned binding of functionalized microspheres for optical diffraction-based biosensors

Brief Summary Paragraph Right (9):
Additionally, biosensors having a self-assembling monolayer have been used to detect analytes and are set forth in U.S. patent application Ser. Nos. 08/768,449 and 08/991,844, both of which are incorporated herein by reference in their entirety. However, these biosensors currently do not have the requisite sensitivity required to detect smaller analytes since these smaller analytes do not produce a sufficient diffraction pattern to be visible.

Detailed Description Paragraph Right (25):
FIG. 2 outlines the procedure used for microcontact printing. An elastomeric stamp is used to transfer analyte-specific receptor "ink" to a gold surface by contact; if the stamp is patterned, a patterned analyte-specific receptor layer forms. The stamp is fabricated by casting polydimethylsiloxane (PDMS) on a master having the inverse of the

desired pattern. Masters are prepared using standard photolithographic techniques, or constructed from existing materials having microscale surface features.

14. Document ID: US 6197515 B1

L19: Entry 14 of 26 File: USPT Mar 6, 2001

US-PAT-NO: 6197515
DOCUMENT-IDENTIFIER: US 6197515 B1

TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

L19: Entry 14 of 26 File: USPT Mar 6, 2001

US-PAT-NO: 6197515
DOCUMENT-IDENTIFIER: US 6197515 B1

TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

DATE-ISSUED: March 6, 2001

US-CL-CURRENT: 435/6

APPL-NO: 9/ 296111
DATE FILED: April 21, 1999

PARENT-CASE:

RELATED APPLICATIONS
This application is a divisional of Ser. No. 08/786,187, filed Jan. 21, 1997, which is a continuation of U.S. patent application Ser. No. 08/312,388, filed Sep. 26, 1994 by Bamdad, et al., now U.S. Pat. No. 5,620,850.

L19: Entry 14 of 26 File: USPT Mar 6, 2001

DOCUMENT-IDENTIFIER: US 6197515 B1
TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

Brief Summary Paragraph Right (38):
The present invention provides yet another method of capturing a biological molecule. This method involves providing a solid phase that has a surface having adhered thereto a species having a formula X--R--Ch--M--BP, in which X represents a functional group that adheres to the surface, R represents a self-assembled monolayer-promoting spacer moiety, Ch represents a chelating agent that coordinates a metal ion, M represents a metal ion coordinated by the chelating agent, and BP represents a binding partner of the biological molecule, coordinated to the metal ion. A target molecule then is allowed to biologically bind to the binding partner. The biological molecule then can be determined, for example by detecting a physical change associated with the surface.

Detailed Description Paragraph Right (44):
The articles of the present invention can be used for a variety of applications, including biosensing applications, test assays, and the like. The term "test assay" generally refers to any procedure in which a member of a biological binding partner pair is to be captured from a medium in which it is dispersed. For example, "test assay" may be used to describe a diagnostic procedure, analytical procedure, microanalytical procedure, forensic analysis, pharmacokinetic study, cell sorting procedure, affinity chromatogram, industrial or laboratory recovery or analysis of one or more species such as toxins, catalysts, or starting materials or products, and the like. a typical test assay is an immunoassay. Biosensing applications include those

such as drug screening, environmental monitoring, medical diagnostics, quality control in the pharmaceutical and food industries, and other areas in which it is advantageous to sensitively determine biological binding between partners.

15. Document ID: US 6180288 B1

L19: Entry 15 of 26 File: USPT Jan 30, 2001

US-PAT-NO: 6180288
DOCUMENT-IDENTIFIER: US 6180288 B1

TITLE: Gel sensors and method of use thereof

L19: Entry 15 of 26 File: USPT Jan 30, 2001

US-PAT-NO: 6180288
DOCUMENT-IDENTIFIER: US 6180288 B1

TITLE: Gel sensors and method of use thereof

DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 430/2; 264/1.1, 422/82.06, 430/1, 430/320, 430/321, 436/531

APPL-NO: 8/ 821464
DATE FILED: March 21, 1997

L19: Entry 15 of 26 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180288 B1
TITLE: Gel sensors and method of use thereof

Brief Summary Paragraph Right (11):
The present invention comprises an optically diffracting sensing device in which a diffraction pattern changes upon exposure to a predetermined stimuli. The diffraction pattern in the sensing device of the present invention may be two or three dimensional, and, in one embodiment, the change in diffraction patterns is recognizable to the untrained eye. The sensing device of the present invention comprises one or more gels coated onto patterned, self-assembling monolayers of alkanethiolates, carboxylic acids, hydroxamic acids, or phosphonic acids printed onto a variety of substrates, including, but not limited to, glass, silicon, aluminum oxide, and thermoplastic films metallized with gold, or with an alloy such as nickel/gold. The present invention also comprises the method of making this device, and the use of this device. In its desired embodiment, the sensing device of the present invention uses white light without any supporting detection or amplification systems.

Brief Summary Paragraph Right (12):
Patterned self-assembling monolayers allow for the controlled placement of gel solutions thereon and which can contain a chemically reactive, indicator functionality. The gels suitable for use in the present invention can be produced by a variety of means, including solvent evaporation, radiation, or chemical cross-linking. When exposed to electromagnetic radiation, such as visible light, the sensing devices of the present invention produce optical diffraction patterns which can change depending on the reaction of the gel with the stimulus of interest. The electromagnetic radiation can be in the visible spectrum, and can be either reflected from the substrate, or transmitted through the substrate. The stimulus to be detected can be any compound that reacts with the gel directly or with an indicator substance contained in the gel. (See, for example, Irie, M., pp. 49-65; Y. Osada and J. Gong) The present invention can be used to measure any stimuli to which a gel will respond, including, but not limited to,

mechanical, temperature, electrical, and chemical stimuli.

Detailed Description Paragraph Right (27):
FIG. 1 outlines the procedure used for microcontact printing onto a substrate. An elastomeric stamp is used to transfer by contact alkanethiol "ink" to a surface coated with a metal alloy. In a desired embodiment, the alloy surface is predominantly gold. Preferred alloys are those such as nickel/gold, which are known to show an enrichment in the surface concentration of gold relative to its bulk concentration. Prediction of surface segregation of one metal of an alloy is described in M. P. Seah, "Quantitative Prediction of Surface Segregation," Journal of Catalysis, vol. 57, pp. 450-457 (1979), and J. J. Burton, et al., "Prediction of Segregation to Alloy Surfaces from Bulk Phase Diagrams," Physical Review Letters, vol. 37, No. 21, pp. 1433-1436 (Nov. 22, 1976), both incorporated herein by reference. In one embodiment of the invention, the metal alloy has surface enrichment of a metal reacting with the self-assembling monolayer. If the stamp is patterned, a patterned self-assembling monolayer forms. The stamp is fabricated by casting polydimethylsiloxane (PDMS) on a master having the desired pattern. Masters are prepared using standard photolithographic techniques, or constructed from existing materials having microscale surface features. These methods are disclosed in U.S. Pat. No. 5,512,131 and copending U.S. patent application Ser. No. 08/707,456 entitled, "Method of Contact Printing on Metal Alloy Coated Polymer Films," and the U.S. patent application entitled, "Method of Contact Printing on Gold Coated Films," filed Dec. 18, 1996, all of which are incorporated herein by reference.

Detailed Description Paragraph Right (90):
Coherent light with wavelength .lambda.=0.6328 micrometers was diffracted by the sample which was enclosed in an environment chamber. The diffraction orders were collected by a lens and imaged onto a CCD camera where the image was displayed on a monitor and stored on a computer for image processing and analysis. This experimental setup was used to measure the two dimensional diffraction image intensity from a self-assembled-monolayer (SAM)-patterned array of temperature-responsive poly-N-isopropylacrylamide (NIPA). The poly-NIPA bumps undergo a volume shrinkage with increasing temperature, therefore, the detected diffraction order irradiance from one spot to the next changed, as was predicted by the model, with a rise in temperature. An example image captured during this experiment is shown below in FIG. 16. The zero order beam in this figure was blocked to eliminate CCD saturation. S. Hirotsu, Y. Hirokawa, and T. Tanaka, "Volume-phase transitions of ionized N-isopropylacrylamide gels," J. Chem. Phys., vol. 87, no. 2, pp. 1392-1394, Jul. 15, 1987, incorporated herein by reference.

16. Document ID: US 6067342 A

L19: Entry 16 of 26 File: USPT May 23, 2000

US-PAT-NO: 6067342
DOCUMENT-IDENTIFIER: US 6067342 A

TITLE: Digital filmless X-ray projection imaging system and method

L19: Entry 16 of 26 File: USPT May 23, 2000

US-PAT-NO: 6067342
DOCUMENT-IDENTIFIER: US 6067342 A

TITLE: Digital filmless X-ray projection imaging system and method

DATE-ISSUED: May 23, 2000

US-CL-CURRENT: 378/19; 378/15, 378/901

APPL-NO: 9/ 074184
DATE FILED: May 7, 1998

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
This application is based upon provisional application, U.S. Ser. No. 60/063,567 filed Oct. 30, 1997.

L19: Entry 16 of 26 File: USPT May 23, 2000

DOCUMENT-IDENTIFIER: US 6067342 A
TITLE: Digital filmless X-ray projection imaging system and method

Brief Summary Paragraph Right (13):
Image Intensifier Tubes (IIT). The film/screen combination used in a conventional X-ray system may be replaced with an IIT. An IIT comprises four primary components: a photo cathode, a microchannel plate, a screen and a housing which holds the other components stationary relative to one another. As X-ray photons which have propagated through a patient strike the photo cathode (essentially a flourescent screen), electrons are emitted into the interior of the tube. The electrons are accelerated to produce a small image on a microchannel plate, which is a second fluorescent screen. The image on the second screen is captured using a video camera with a digital output, such as a CCD camera. The resulting system receives an X-ray beam and produces a direct digital output. However, the spatial resolution and dynamic range of an IIT based system are typically less than conventional film. IIT-based systems are commonly found in cardiac scanners. An exemplary IIT is described in U.S. Pat. No. 3,708,673, entitled IMAGE INTENSIFIER TUBE, invented by Blacker et al., and assigned to The Machlett Laboratories, Inc., of Springdale, Conn.

Detailed Description Paragraph Right (7):
Each fan beam section preferably strikes a corresponding detector of the detector assembly 106. In the embodiment shown the detectors are disposed parallel to one another. Each detector is preferably defined by a scintillator 306, the scintillators 306 being arranged as a 1D array and forming the next layer of the detector assembly 106. Each collimated fan beam section strikes the portion of the corresponding scintillator 306 exposed through the aperture 206 and between the collimator plates 304. Thus, an array of individual scintillators is placed in correspondence with the collimators so that each collimated fan beam section passes between two adjacent collimator plates and irradiates the portion of the corresponding scintillator 306 exposed through the aperture 206. Each scintillator preferably comprises a rectangular parallelepiped of material that converts X-ray photons to optical photons. In a preferred embodiment, the scintillators 306 include cadmium tungstate (CdWO.sub.4), although other materials suitable for converting X-ray energy to light energy may be used. The number and density of detectors can vary depending on the application, the ultimate resolution of the image, and limitations relating to cost of the system. In one embodiment of the invention, the number of scintillators is approximately 2000, and the width of each detector (defining the density of the detectors) is approximately 100-200 microns. Thus, the described embodiment requires approximately 2000 scintillators, versus approximately 2000.sup.2 for a prior art system employing a two dimensional square matrix array of semiconductor detectors, reducing the number of scintillators by 3,998,000. Very clearly, depending upon the application, any number and density of detectors can be utilized, with as little as 100 to 500 (or even less depending on the application), each having a width on the order of 0.5 cm (or even larger depending on the application) still providing relatively good data.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

17. Document ID: US 5977567 A

L19: Entry 17 of 26 File: USPT Nov 2, 1999

US-PAT-NO: 5977567

DOCUMENT-IDENTIFIER: US 5977567 A

TITLE: Optoelectronic assembly and method of making the same
L19: Entry 17 of 26 File: USPT Nov 2, 1999

US-PAT-NO: 5977567
DOCUMENT-IDENTIFIER: US 5977567 A

TITLE: Optoelectronic assembly and method of making the same

DATE-ISSUED: November 2, 1999

US-CL-CURRENT: 257/99; 257/432, 257/680, 257/701, 257/81, 257/82

APPL-NO: 9/ 003114
DATE FILED: January 6, 1998
L19: Entry 17 of 26 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5977567 A
TITLE: Optoelectronic assembly and method of making the same

Brief Summary Paragraph Right (20):
These objects and advantages are achieved by an optoelectronic assembly having an insulating substrate with a planar surface and a metal layer bonded to the planar surface such that selected regions of the substrate are exposed and a step is produced between the substrate and a top surface of the metal layer. An active optical device such as a diode laser, optical amplifier, optical modulator, light detector or any other device is mounted on the metal layer. The active device has a first optical axis and in this arrangement this axis is parallel to the substrate. In addition, the metal layer provides an electrical path to the active device. It is essential for the optoelectronic assembly that the metal layer have a well-defined thickness. This thickness is selected such that the heat generated by the active device is dissipated, the substrate does not interfere with the propagation of light along the first optical axis, and such that the in-plane coefficient of thermal expansion (CTE) of the metal layer is constrained by the substrate.

Brief Summary Paragraph Right (24):
A bottom metal layer can be bonded to the insulating substrate opposite the planar surface. This second layer can also be patterned as a n electrical circuit. In on e embodiment the assembly with such a second layer has no cooling elements mounted on the opposite side of the substrate. These cooling elements may include Peltier coolers. Micro-channel coolers using fluid coolants can also be patterned in the second layer of metal.

18. Document ID: US 5922550 A
L19: Entry 18 of 26 File: USPT Jul 13, 1999

US-PAT-NO: 5922550
DOCUMENT-IDENTIFIER: US 5922550 A

TITLE: Biosensing devices which produce diffraction images
L19: Entry 18 of 26 File: USPT Jul 13, 1999

US-PAT-NO: 5922550
DOCUMENT-IDENTIFIER: US 5922550 A

TITLE: Biosensing devices which produce diffraction images

DATE-ISSUED: July 13, 1999

US-CL-CURRENT: 435/7.21; 435/287.1, 435/287.2, 436/501, 536/120

APPL-NO: 8/ 768449
DATE FILED: December 18, 1996
L19: Entry 18 of 26 File: USPT Jul 13, 1999

DOCUMENT-IDENTIFIER: US 5922550 A
TITLE: Biosensing devices which produce diffraction images

Brief Summary Paragraph Right (10):
The present invention includes a support for a self-assembling monolayer on gold or other suitable material which does not require an adhesion promoter for the formation of a well-ordered self-assembling monolayer. The present invention also provides a support for a self-assembling monolayer on gold or other material which is suitable for continuous printing, rather than batch, fabrication. In addition, the present invention provides a low-cost, disposable biosensor which can be mass produced. The biosensors of the present invention can be produced as a single test for detecting an analyte or it can be formatted as a multiple test device. The biosensors of the present invention can be used to detect contamination in garments, such as diapers, and to detect contamination by microorganisms.

Brief Summary Paragraph Right (11):
In another embodiment of the present invention, nutrients for a specific class of microorganisms can be incorporated into the self assembling monolayer. In this way, very low concentrations of microorganisms can be detected by first contacting the biosensor of the present invention with the nutrients incorporated therein and then incubating the biosensor under conditions appropriate for the growth of the bound microorganism. The microorganism is allowed to grow until there are enough organisms to form a diffraction pattern.

Detailed Description Paragraph Right (4):
The self-assembling monolayer on the metalized film contains a receptive material, such as an antibody, that will specifically bind to an epitope on the analyte that is different from the epitope used in the binding to the particle. Thus, for detecting a medium with a small analyte, such as viral particles, the medium is first exposed to the latex particles to which the viral particles bind. Then, the latex particles are optionally washed and exposed to the metalized film with the self-assembling monolayers containing the virus specific antibodies. The antibodies then bind to the viral particles on the latex bead thereby immobilizing the latex beads in the same pattern as the monolayers on the film. Because the bound latex beads will cause diffraction of the visible light, a diffraction pattern is formed, indicating the presence of the viral particle in the liquid. Other combinations using particles are well known to those of ordinary skill in the art.

Detailed Description Paragraph Right (6):
In another embodiment of the present invention, nutrients for a specific class of microorganisms can be incorporated into the self assembling monolayer. In this way, very low concentrations of microorganisms can be detected by first contacting the biosensor of the present invention with the nutrients incorporated therein and then incubating the biosensor under conditions appropriate for the growth of the bound microorganism. The microorganism is allowed to grow until there are enough organisms to form a diffraction pattern. Of course, in some cases, the microorganism can multiply enough to form a diffraction pattern without the presence of a nutrient on the patterned monolayer.

Detailed Description Paragraph Right (19):
In another embodiment of the present invention, a multiple analyte test is constructed on the same support. As shown in FIG. 1, a strip 10 is provided with several micro-contact printed metalized films 20, 25, 30 and 35, each film having a self-assembled monolayer pattern 40 printed thereon. Each of the micro-contact printed metalized films 15, 20, 25, and 30 have a different receptive material that is

different for different analytes. It can be seen that the present invention can be formatted in any array with a variety of micro-contact printed metalized films thereby allowing the user of the biosensor device of the present invention to detect the presence of multiple analytes in a medium using a single test.

Detailed Description Paragraph Right (23):
FIG. 2 outlines the procedure used for microcontact printing. An elastomeric stamp is used to transfer alkanethiol "ink" to a gold surface by contact; if the stamp is patterned, a patterned self-assembling monolayer forms. The stamp is fabricated by casting polydimethylsiloxane (PDMS) on a master having the desired pattern. Masters are prepared using standard photolithographic techniques, or constructed from existing materials having microscale surface features.

19. Document ID: US 5856235 A

L19: Entry 19 of 26 File: USPT Jan 5, 1999

US-PAT-NO: 5856235
DOCUMENT-IDENTIFIER: US 5856235 A

TITLE: Process of vacuum annealing a thin film metallization on high purity alumina

L19: Entry 19 of 26 File: USPT Jan 5, 1999

US-PAT-NO: 5856235
DOCUMENT-IDENTIFIER: US 5856235 A

TITLE: Process of vacuum annealing a thin film metallization on high purity alumina

DATE-ISSUED: January 5, 1999

US-CL-CURRENT: 438/648; 438/650, 438/656, 438/660

APPL-NO: 8/ 421809
DATE FILED: April 12, 1995

L19: Entry 19 of 26 File: USPT Jan 5, 1999

DOCUMENT-IDENTIFIER: US 5856235 A
TITLE: Process of vacuum annealing a thin film metallization on high purity alumina

Brief Summary Paragraph Right (6):
To maintain an interconnect directly behind each pixel in the Z direction the module layers must be kept very thin, usually less than one pixel center-to-center spacing. The layers, which are ceramic substrates having thin-film microcircuits printed thereupon, are laminated using extremely thin thermal setting adhesive sheets. A principal shortcoming to this laminated multi-layer assembly is the poor dimension stability that exists due to a mismatch of the coefficients of expansion between the ceramic layers and the thermal set adhesive sheets. To alleviate this problem in the past, a thermal-stress barrier commonly known as a buffer board, was used to absorb the thermal stress from the module. The buffer board was placed between the infrared detector arrays and the module and thus provides for electrical and mechanical interconnection therebetween.

Brief Summary Paragraph Right (10):
More specifically, in the Z-technology ceramic multi-chip modules, thin-film materials are sputter deposited onto thin-film grade alumina (99.6% Al.sub.2 O.sub.3) substrates and delineated to form the required microchip patterns. Sputtering is a process in which material is removed from a source (the cathode) and accelerated through a plasma

and deposited on the substrate (the anode). Then individual pattern layers are laminated together to form a multi-layer Z-module using a glass fusion-lamination technique, as described in Hornback, U.S. Pat. No. 5,128,749. The fusion-lamination process uses low temperature firable glass at temperatures as high as 600.degree. C. with pressure up to 300 kN/m.sup.2. Under these conditions, however, microcircuits made with sputtered thin-film materials have failed on the conventional substrates due to the factors described above.

20. Document ID: US RE35884 E

L19: Entry 20 of 26 File: USPT Sep 1, 1998

US-PAT-NO: RE35884
DOCUMENT-IDENTIFIER: US RE35884 E

TITLE: Flexible lead assembly for microchannel plate-based detector

L19: Entry 20 of 26 File: USPT Sep 1, 1998

US-PAT-NO: RE35884
DOCUMENT-IDENTIFIER: US RE35884 E

TITLE: Flexible lead assembly for microchannel plate-based detector

DATE-ISSUED: September 1, 1998

US-CL-CURRENT: 250/336.1; 250/207, 250/214VT, 250/397, 313/103CM, 313/105CM, 361/749

APPL-NO: 8/ 806495
DATE FILED: February 20, 1997

REISSUE-DATA:

US-PAT-NO	DATE-ISSUED	APPL-NO	DATE-FILED
05391874	February 21, 1995	106945	August 17, 1993

L19: Entry 20 of 26 File: USPT Sep 1, 1998

DOCUMENT-IDENTIFIER: US RE35884 E
TITLE: Flexible lead assembly for microchannel plate-based detector

Abstract Paragraph Left (1):
A microchannel plate (MCP)-based detector of reduced size employs a flexible multilayer printed circuit board as a lead assembly and enjoys increased ease of assembly and improved versatility.

Brief Summary Paragraph Right (1):
The invention relates to microchannel plate (MCP) based detectors. In particular, the invention pertains to MCP-based detectors of reduced size and simplified manufacture having flexible electrical leads. The invention is especially useful in detectors for scanning electron microscopes (SEM), but is also useful in detectors for other applications.

Brief Summary Paragraph Right (3):
The majority of MCP detectors for high gain applications are constructed by stacking a series of ceramic insulators, metal electrical contacts, MCPs and anodes in a specific configuration to achieve the proper spacing and alignment necessary for a functional detector. FIGS. 1A and 1B illustrate typical arrangements of known microchannel plate detectors. In FIG. 1A, the detector 10 has an aperture 11 through which an electron

beam 12 is directed at a sample S. Back-scattered and secondary electrons 12' are detected. The detector 10 is a stacked arrangement including opposed housing elements 13 and 14, insulator 16, metal contact tab assemblies 18, anodes 20 and a pair of MCPs, namely input MCP 22A and output MCP 22B, in abutting relation having respective channels 24A and 24B disposed at an angle with respect to the detector axis 26 to form a chevron structure for reducing ion feedback. A shielded wiring harness 27 containing high voltage leads and anode leads 28 is employed to reduce noise. In particular, the anode leads are coaxial cables and an outer braided sheath 30 is employed as a ground.

Brief Summary Paragraph Right (8):
Each layer in the detector has a separate function, and one or more assorted small parts are required for each layer of the assembly. The total number of parts required to assemble a conventional MCP-based detector is high. For example, thirty-one (31) parts are required for the detector 10, shown in FIG. 1A. Assembly of the device and the shielded harness is difficult and time consuming. Also, each of the many parts is made to high tolerance. Thus, the inventory required to achieve normal production is costly to maintain and control.

Brief Summary Paragraph Right (11):
In one embodiment, the invention is directed to a detector for a scanning electron microscope (SEM). The detector comprises at least one microchannel plate (MCP) having input and output faces and a flexible lead assembly having a detector end, a connector end and intermediate lead portion. The detector end of the flexible lead assembly includes an electrode coupled to each face of the MCP and at least one anode for carrying output signals from the MCP. The flexible lead assembly is formed of alternating stacked layers of dielectric and electrically conductive material, one conductive layer for each of the electrodes and the anode.

Brief Summary Paragraph Right (12):
In a particular embodiment of the invention, the detector comprises a stack of microchannel plates (MCPs); a flexible lead assembly including a detector end, a high voltage connector end and an intermediate lead portion; and hardware to secure the MCPs to the detector end of the lead assembly. The detector end of the flexible lead assembly includes high voltage electrodes for contacting the input and output faces of the MCP stack and at least one anode for collecting the amplified signal from the MCPs. The intermediate lead portion and the connector end of the flexible assembly are made up of multiple layers of electrically conductive metal traces separated by, and bonded to, insulating layers of dielectric. Additional layers of dielectric and electrically conductive traces are employed to provide shielding in the intermediate portion.

Detailed Description Paragraph Right (1):
The invention is generally directed to an areal detector for ions, electrons, UV photons and soft X-rays which utilizes a multilayer flexible circuit board as an integrated lead assembly. In a particular exemplary embodiment illustrated in FIGS. 2-7, the invention pertains to a microchannel plate (MCP)-based detector 50 employing a stack 51 of back-to-back microchannel plates 52A and 52B having an input face 53A and output face 53B, a multilayer flexible lead assembly 54 and hardware 56 to secure the MCPs to the lead assembly. The flexible lead assembly 54 shown in the plan view of FIG. 2 is an integrated multilayer laminated structure formed with a detector end 58, a high voltage connector end 60 and an intermediate lead portion 62. The invention is designed to operate in high-vacuum and all components are high-vacuum compatible.

Detailed Description Paragraph Right (4):
In the MCP-based detector 50, the stack 51 of microchannel plates 52A and 52B (MCPs) is sandwiched between the high voltage input electrode and high voltage output electrode layers 64 and 66 and the anode layer 68 is positioned adjacent the output electrode layer 66 facing the output face 53B of the stack 51, as seen in FIG. 5. The electrode layers 64 and 66, anode 68 and the MCP stack 51 at detector end 58 of the flexible lead assembly 54 are held together with the mechanical hardware 56 which comprises an annular ring 90 at the input side and an apertured backing plate 92 adjacent the anode, as seen in FIG. 3. In the embodiment illustrated, the MCPs 52A and 52B are each formed with a corresponding central aperture 94 aligned along a common central axis 95 of the stack 51. The backing plate 92 is formed with a central tube 96 which extends into the aperture 87 in the anode layer 68 and the aperture 94 in the MCPs along the central axis 95. Alternatively, the MCPs and the backing plate may be formed without the central apertures or the tube.

CLAIMS:

1. An areal detector for both charged and neutral particles and energetic photons comprising: at least one microchannel plate (MCP) having a signal input face and signal output face; a flexible circuit having a detector end, an intermediate electrical lead portion with electrical shielding means and a connector end, and means for supporting said at least one MCP in said detector end of the flexible circuit; said flexible circuit including a pair of electrodes one each coupled to the respective signal input face and signal output face of said at least one MCP and at least one anode for collecting electron current signals from the signal output face of said at least one MCP.

15. A detector comprising: a microchannel plate (MCP) having electrically conductive input and output faces and an integrated multilayer flexible circuit having a detector end, a connector end and intermediate lead portion with electrical shielding means, said flexible circuit including an electrode layer for each face of the MCP and at least one anode for receiving signals from the output face of the MCP.

22. A lead assembly for a microchannel plate (MCP)-based detector comprising an integrated multilayer flexible circuit having a detector end, a connector end and intermediate lead portion, said flexible circuit including an electrode layer for each face of the MCP and at least one anode for receiving signals from the output face of the MCP. .Iadd.

23. An areal detector for both charged and neutral particles and energetic photons comprising: at least one microchannel plate (MCP) having a signal input face and signal output face; a flexible circuit having a detector end, an intermediate electrical lead portion and a connector end, and means for supporting said at least one MCP in said detector end of the flexible circuit; said flexible circuit including a plurality of electrodes one each coupled to the respective signal input face and signal output face of said at least one MCP and at least one anode for collecting electron current signals from the signal output face of said at least one MCP..Iaddend..Iadd.24. The detector of claim 23, wherein the intermediate lead portion includes at least one anode lead connecting the anode to the connector end..Iaddend..Iadd.25. The detector of claim 24, wherein the intermediate lead portion includes electrical shielding means substantially surrounding a portion of the at least one anode lead in the intermediate electrical lead portion..Iaddend..Iadd.26. The detector of claim 24 further including electrical grounding surrounding the electrodes in the intermediate lead portion..Iaddend..Iadd.27. A lead assembly for a microchannel plate (MCP)-based detector comprising: a flexible circuit having a detector end, a connector end and intermediate lead portion, said flexible circuit including an electrode layer for each face of the MCP and at least one anode..Iaddend..Iadd.28. A lead assembly for a microchannel plate (MCP)-based detector comprising: a plurality of flexible circuit layers each including a detector end, a connector end and intermediate lead portion arranged as a stacked array for engaging the MCP..Iaddend..Iadd.29. The detector of claim 28 wherein the stacked array comprises single flexible circuit layers..Iaddend..Iadd.30. The detector of claim 28 wherein each flexible circuit layer includes a conductive trace extending from the detector end to the connector end..Iaddend..Iadd.31. A lead assembly for a microchannel plate (MCP)-based detector comprising: a plurality of flexible circuit layers each including a detector end, a connector end and intermediate lead portion, said flexible circuit layers each including at least one of an electrode layer for a corresponding face of the MCP and an anode layer for receiving signals from the output face of the MCP..Iaddend..Iadd.32. The detector of claim 31 wherein the lead assembly comprises a stacked array of the flexible circuit layers..Iaddend..Iadd.33. The detector of claim 31 wherein each assembly comprises a stacked array of single flexible circuit layers..Iaddend..Iadd.34. The detector of claim 31 wherein each flexible circuit layer includes a conductive trace extending from the detector end

to the connector end..Iaddend..Iadd.35. A lead arrangement for a microchannel plate (MCP)-based detector having an anode face and bias electrodes comprising:

at least one flexible anode circuit for the MCP including a detector end and an anode thereat for positionment in operative relationship with the anode face;

a connector end; and

an intermediate lead portion and an anode lead electrically connecting the anode and the connector end; and

at least one flexible electrode circuit for positionment in operative relationship with

the bias electrodes including an electrode end and an electrode thereat;

a connector end; and

an intermediate lead portion and an electrode lead electrically connecting the electrode and the connector end..Iaddend.

21. Document ID: US 5776674 A

L19: Entry 21 of 26 File: USPT Jul 7, 1998

US-PAT-NO: 5776674
DOCUMENT-IDENTIFIER: US 5776674 A

TITLE: Chemical biochemical and biological processing in thin films

L19: Entry 21 of 26 File: USPT Jul 7, 1998

US-PAT-NO: 5776674
DOCUMENT-IDENTIFIER: US 5776674 A

TITLE: Chemical biochemical and biological processing in thin films

DATE-ISSUED: July 7, 1998

US-CL-CURRENT: 435/6; 356/364, 435/5, 435/7.1, 435/7.2, 435/7.9, 435/91.1, 436/172, 436/518, 436/527, 436/543, 436/547, 530/333, 530/334, 530/388.1, 536/24.3, 536/24.32, 536/24.33

APPL-NO: 8/ 462485
DATE FILED: June 5, 1995

L19: Entry 21 of 26 File: USPT Jul 7, 1998

DOCUMENT-IDENTIFIER: US 5776674 A
TITLE: Chemical biochemical and biological processing in thin films

Detailed Description Paragraph Right (14):
Various features such as wells 102, 104 may be formed in the solid substrate to facilitate the placement and separation of reagent droplets as illustrated in the side views of FIGS. 3B and 3C. Such features can be formed in the substrate by various means including lithography and etching, stamping or molding, or micromachining. Such a pre-formed substrate may be coated with the thin film as described above, and then the various sample wells, micro channels or microchambers loaded with their proper reagents through the thin film coating, or the reagent chambers may be loaded first and then the thin film coating applied. The reagents may include various agents to increase their density above that of the thin film so that the reagent will settle into the depression in the substrate and displace the film. This is similar to the manner in which the well of an electrophoresis gel is typically loaded. Indicator dyes are often added to such reagents in order to more easily visualize the loading process. Such dyes, if used, must obviously be compatible with the reagent and any processing step which is to occur in that reagent location. A particle can be moved vertically with the optical trap to introduce it to the reagent pool and then vertically withdrawn for horizontal transport to adjacent reagent locations via the thin film. If optical trapping is to be performed through a substrate containing pre-formed features (i.e., not optically flat) such as wells 102 of FIG. 3B or 104 of FIG. 3C, those features must be designed and fashioned in such a manner that they do not interfere with the trapping beam. For example, abrupt vertical changes in surface features are to be avoided. If optical trapping is to be performed from the thin film side, such constraints are less important as depicted in

FIG. 3C.

Detailed Description Paragraph Right (40):
It is desirable to minimize the two-dimensional diffusion of individual cleaved nucleotides across the surface so as to permit the closest possible spacing of cleaved nucleotides without scrambling their proper sequential order (Pratt and Keller, supra). A variety of means can be employed to minimize diffusion. One of the simplest is to increase the viscosity of the liquid surface film as outlined above and control the spacing of released single nucleotides by appropriately regulating the turnover number of the exonuclease (e.g., by varying the temperature) and the rate of translation of the single DNA molecule through the thin film. In addition, it is possible to cross-link a polymer film on the surface in the trail behind the DNA containing the single nucleotides by following the path with a second focused laser beam which photo-crosslinks the polymer but does not photobleach the released single nucleotides. With the right selection of polymer, it is possible to photo-crosslink with the infrared trapping beam if the cross-linking time is adjusted to be long enough to allow the extended DNA chain to pass first. It is also possible to modify the surface chemistry of the substrate so as to provide very high binding capacity for nucleotide monophosphates, for example, through electrostatic interactions with the negatively charged phosphate group (Matheja and Degens, "Structural Molecular Biology of Phosphates", Fortschritte Der Evolutionsforschung, Band V, Gustav Fischer Verlag, Stuttgart, 1971, pp. 180, which is incorporated herein by reference). Anion exchange reagents typically used to bind nucleotide monophosphates may be employed. Alternatively, proteins or organic and inorganic complexing agents (Kyogoku, Lord and Rich, Proc. Natl. Acad. Sci. USA, 57:250-257 (1967); Kyogoku, Lord and Rich, Nature 218:69-72 (1968); Kim and Rich, Proc. Natl. Acad. Sci. USA, 60:402-408 (1968); Terron and Moreno, Inorganica Chimica Acta 56:L57-L59 (1981), which are incorporated herein by reference) which specifically bind to the different nucleotide monophosphates can be bound to the substrate surface, serving as effective traps for the released mononulceotides. Self-assembled monolayers on the substrate can be utilized to provide such nucleotide binding capacity. The oriented nature of such self-assembled monolayers will also serve to orient the bound nucleotides to facilitate detection.

Detailed Description Paragraph Right (48):
Signal 337 is used to synchronize the mode-locked frequency of the laser with a sinusoidal voltage generator 380 to trigger high voltage sweeps across orthogonal electrode pairs, one pair of which is shown as electrodes 382A and B in FIG. 5 and the other pair of which is at right angles thereto. Advantageously, the sweep frequency is such that only a single sweep takes place between successive laser pulses. The single photo-electron emitted when the single fluorescent photon strikes photo-cathode 375 is accelerated in the high vacuum inside the streak tube by extraction grid 377 and experiences a unique electrical field that is a function of the time of emission of the single photon after the laser pulse. As a result, the single photo-electron strikes microchannel plate 385 at a point along the y-axis proportional to its emission time. Accordingly, the spatial coordinates of the photoelectron incident on micro-channel plate 385 are representative of the delay time and wavelength of each detected photon. These coordinates are digitized by digitizer 390 and provided to computer 400.

22. Document ID: US 5712483 A

L19: Entry 22 of 26 File: USPT Jan 27, 1998

US-PAT-NO: 5712483
DOCUMENT-IDENTIFIER: US 5712483 A

TITLE: X-ray grid-detector apparatus

L19: Entry 22 of 26 File: USPT Jan 27, 1998

US-PAT-NO: 5712483
DOCUMENT-IDENTIFIER: US 5712483 A

TITLE: X-ray grid-detector apparatus

DATE-ISSUED: January 27, 1998

US-CL-CURRENT: 250/367; 250/368, 250/486.1, 250/487.1

APPL-NO: 8/ 672633
DATE FILED: June 28, 1996
L19: Entry 22 of 26 File: USPT Jan 27, 1998

DOCUMENT-IDENTIFIER: US 5712483 A
TITLE: X-ray grid-detector apparatus

Abstract Paragraph Left (1):
A hybrid grid-detector apparatus for x-ray systems wherein a microchannel plate structure has an air-interspaced grid portion and a phosphor/optical fluid-filled grid portion. The grids are defined by multiple adjacent channels separated by lead-glass septa. X-rays entering the air-interspaced grid portion at an angle of impingement upon the septa are attenuated, while non-impinging x-rays pass through to the phosphor/fluid filled portion. X-ray energy is converted to luminescent energy in the phosphor/fluid filled portion and the resultant beams of light are directed out of the phosphor/optical fluid filled portion to an imaging device.

Brief Summary Paragraph Right (11):
By way of example, and not of limitation, the invention increases the efficiency of x-ray absorption, or detection efficiency, by using an efficient air interspaced grid design and thick x-ray absorbing phosphor. The phosphor is housed in very small light channeling pores of a microchannel plate (MCP), which provide for only minimal lateral light spread while maintaining spatial resolution even with substantially thicker phosphor layers than are normally used. Furthermore, instead of using a light-attenuating binder as in traditional screens, the phosphor crystals are tightly packed into the pores of the MCP, and the pores are then filed with optical fluid. The fluid has an index of refraction matched to the extent possible to that of the phosphor crystals so as to substantially reduce optical scattering interfaces and improve light output.

Detailed Description Paragraph Right (2):
Referring first to FIG. 1 through FIG. 3, a grid detector apparatus in accordance with the present invention generally comprises a layered assembly of microchannel plates fabricated from glass containing lead oxide or a like material having a high atomic number which attenuates the transmittal of x-rays therethrough. Each microchannel plate comprises a generally grid-shaped structure with very small channels, or pores, defined by thin walls of the lead glass material. Such microchannel plates can be fabricated to exhibit the characteristics described below, or can be obtained from commercial sources such as Schott Company in Germany and Collimated Holes, Inc., in Santa Barbara, Calif. An example of a grid assembly and method of manufacturing the same suitable for use in the present invention is described in U.S. Pat. No. 5,455,849 entitled "Air-Core Grid For Scattered X-Ray Rejection", issued on Oct. 2, 1995 and assigned to the assignee hereof, which is incorporated by reference herein.

Detailed Description Paragraph Right (3):
In the embodiment shown, the invention is depicted with a grid pattern of channels having a square cross-section. However, it will be appreciated that the channels could have other cross-sectional shapes, and that the grid pattern could have a hexagonal, triangular, annular or other shape without departing from the present invention. In addition, the microchannel plates may be planar or slightly arcuate so as to allow the channels to point to a small x-ray source spot.

Detailed Description Paragraph Right (8):
Those skilled in the art will appreciate that, instead of a layered assembly of microchannel plates, the present invention could alternatively be fabricated from a single microchannel plate. In this embodiment, each channels would be separated into two contiguous sections, with one section of each channel being air-filled and the other section of each channel being filled with the phosphor and optical fluid. This integrated configuration has the advantage that the channels and walls will be

perfectly aligned, with an improvement in DQE since the attenuating septa in the anti-scatter grid will not partially block the channels in the scintillating grid.

Detailed Description Paragraph Right (15):
Referring now to FIG. 6 through FIG. 10, a CCD, CMOS camera, silicon photodiode, conventional film detector, lens or other imaging device can be positioned adjacent to, or focused on, the scintillating grid 22 to form a complete image detection apparatus. In the example shown in FIG. 6, first plate 10, second plate 22, first membrane 32, second membrane 34 and a light detector 42 are shown bonded as a multi-layer assembly. In FIG. 7, a complete imaging system is schematically shown which the present invention is positioned between an x-ray source 44 and a light detector 42. While light detector 42 is shown separated from scintillating grid 22, it will be appreciated that the assembly shown in FIG. 6 could be employed as well. FIG. 8 shows an alterative embodiment of the system shown in FIG. 7 wherein a focusing lens 46 is positioned between the light detector 42 and the present invention. Such a configuration would permit the use of a CCD, for example, that is smaller and less costly. In FIG. 9, an alternative embodiment of the system shown in FIG. 7 includes a fiber optic boule reducer 48 positioned between the light detector 42 and the present invention as collimating/focusing device.

CLAIMS:

26. A grid-detector apparatus for x-ray imaging, comprising:

a first microchannel plate having a plurality of air-filled channels;

(b) a second microchannel plate, said second microchannel plate have first and second sides, said first side positioned adjacent to said first microchannel plate, said second microchannel plate having a plurality of phosphor-filled cells;

(c) a reflective membrane layer positioned between said first and second microchannel plates; and

(d) a non-reflective membrane layer positioned adjacent said second side of said second microchannel plate;

(e) said first microchannel plate comprising a first wall structure defining said air-filled channels therein;

(f) said second microchannel plate comprising a second wall structure defining said phosphor-filled cells therein;

(g) said first and second wall structures comprising glass containing a material of an atomic number capable of attenuating x-rays;

(h) said first and second wall structures having walls having a thickness ranging from approximately 5 .mu.m to approximately 800 .mu.m, said air-filled cells and said phosphor-filled cells having a width ranging from approximately 20 .mu.m to approximately 200 .mu.m.

23. Document ID: US 5620850 A

L19: Entry 23 of 26 File: USPT Apr 15, 1997

US-PAT-NO: 5620850
DOCUMENT-IDENTIFIER: US 5620850 A

TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

L19: Entry 23 of 26 File: USPT Apr 15, 1997

US-PAT-NO: 5620850
DOCUMENT-IDENTIFIER: US 5620850 A

TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

DATE-ISSUED: April 15, 1997

US-CL-CURRENT: 530/300; 422/69, 435/4, 435/6, 435/7.1, 435/7.2, 435/7.9, 530/345, 530/388.1, 530/400, 534/15, 534/16

APPL-NO: 8/ 312388
DATE FILED: September 26, 1994
L19: Entry 23 of 26 File: USPT Apr 15, 1997

DOCUMENT-IDENTIFIER: US 5620850 A
TITLE: Molecular recognition at surfaces derivatized with self-assembled monolayers

Brief Summary Paragraph Right (38):
The present invention provides yet another method of capturing a biological molecule. This method involves providing a solid phase that has a surface having adhered thereto a species having a formula X--R--Ch--M--BP, in which X represents a functional group that adheres to the surface, R represents a self-assembled monolayer-promoting spacer moiety, Ch represents a chelating agent that coordinates a metal ion, M represents a metal ion coordinated by the chelating agent, and BP represents a binding partner of the biological molecule, coordinated to the metal ion. A target molecule then is allowed to biologically bind to the binding partner. The biological molecule then can be determined, for example by detecting a physical change associated with the surface.

Detailed Description Paragraph Right (36):
The articles of the present invention can be used for a variety of applications, including biosensing applications, test assays, and the like. The term "test assay" generally refers to any procedure in which a member of a biological binding partner pair is to be captured from a medium in which it is dispersed. For example, "test assay" may be used to describe a diagnostic procedure, analytical procedure, microanalytical procedure, forensic analysis, pharmacokinetic study, cell sorting procedure, affinity chromatogram, industrial or laboratory recovery or analysis of one or more species such as toxins, catalysts, or starting materials or products, and the like. A typical test assay is an immunoassay. Biosensing applications include those such as drug screening, environmental monitoring, medical diagnostics, quality control in the pharmaceutical and food industries, and other areas in which it is advantageous to sensitively determine biological binding between partners.

24. Document ID: US 5391874 A
L19: Entry 24 of 26 File: USPT Feb 21, 1995

US-PAT-NO: 5391874
DOCUMENT-IDENTIFIER: US 5391874 A

TITLE: Flexible lead assembly for microchannel plate-based detector
L19: Entry 24 of 26 File: USPT Feb 21, 1995

US-PAT-NO: 5391874
DOCUMENT-IDENTIFIER: US 5391874 A

TITLE: Flexible lead assembly for microchannel plate-based detector

DATE-ISSUED: February 21, 1995

US-CL-CURRENT: 250/336.1; 250/207, 250/214VT, 250/397, 313/103CM, 313/105CM, 361/749

APPL-NO: 8/ 106945
DATE FILED: August 17, 1993
L19: Entry 24 of 26 File: USPT Feb 21, 1995

DOCUMENT-IDENTIFIER: US 5391874 A
TITLE: Flexible lead assembly for microchannel plate-based detector

Abstract Paragraph Left (1):
A microchannel plate (MCP)-based detector of reduced size employs a flexible multilayer printed circuit board as a lead assembly and enjoys increased ease of assembly and improved versatility.

Brief Summary Paragraph Right (1):
The invention relates to microchannel plate (MCP) based detectors. In particular, the invention pertains to MCP-based detectors of reduced size and simplified manufacture having flexible electrical leads. The invention is especially useful in detectors for scanning electron microscopes (SEM), but is also useful in detectors for other applications.

Brief Summary Paragraph Right (3):
The majority of MCP detectors for high gain applications are constructed by stacking a series of ceramic insulators, metal electrical contacts, MCPs and anodes in a specific configuration to achieve the proper spacing and alignment necessary for a functional detector. FIGS. 1A and 1B illustrate typical arrangements of known microchannel plate detectors. In FIG. 1A, the detector 10 has an aperture 11 through which an electron beam 12 is directed at a sample S. Back-scattered and secondary electrons 12' are detected. The detector 10 is a stacked arrangement including opposed housing elements 13 and 14, insulator 16, metal contact tab assemblies 18, anodes 20 and a pair of MCPs, namely input MCP 22A and output MCP 22B, in abutting relation having respective channels 24A and 24B disposed at an angle with respect to the detector axis 26 to form a chevron structure for reducing ion feedback. A shielded wiring harness 27 containing high voltage leads and anode leads 28 is employed to reduce noise. In particular, the anode leads are coaxial cables and an outer braided sheath 30 is employed as a ground.

Brief Summary Paragraph Right (8):
Each layer in the detector has a separate function, and one or more assorted small parts are required for each layer of the assembly. The total number of parts required to assemble a conventional MCP-based detector is high. For example, thirty-one (31) parts are required for the detector 10, shown in FIG. 1A. Assembly of the device and the shielded harness is difficult and time consuming. Also, each of the many parts is made to high tolerance. Thus, the inventory required to achieve normal production is costly to maintain and control.

Brief Summary Paragraph Right (11):
In one embodiment, the invention is directed to a detector for a scanning electron microscope (SEM). The detector comprises at least one microchannel plate (MCP) having input and output faces and a flexible lead assembly having a detector end, a connector end and intermediate lead portion. The detector end of the flexible lead assembly includes an electrode coupled to each face of the MCP and at least one anode for carrying output signals from the MCP. The flexible lead assembly is formed of alternating stacked layers of dielectric and electrically conductive material, one conductive layer for each of the electrodes and the anode.

Brief Summary Paragraph Right (12):
In a particular embodiment of the invention, the detector comprises a stack of microchannel plates (MCPs); a flexible lead assembly including a detector end, a high voltage connector end and an intermediate lead portion; and hardware to secure the MCPs to the detector end of the lead assembly. The detector end of the flexible lead assembly includes high voltage electrodes for contacting the input and output faces of the MCP stack and at least one anode for collecting the amplified signal from the MCPs. The intermediate lead portion and the connector end of the flexible assembly are made

up of multiple layers of electrically conductive metal traces separated by, and bonded to, insulating layers of dielectric. Additional layers of dielectric and electrically conductive traces are employed to provide shielding in the intermediate portion.

Detailed Description Paragraph Right (1):
The invention is generally directed to an areal detector for ions, electrons, UV photons and soft X-rays which utilizes a multilayer flexible circuit board as an integrated lead assembly. In a particular exemplary embodiment illustrated in FIGS. 2-7, the invention pertains to a microchannel plate (MCP)-based detector 50 employing a stack 51 of back-to-back microchannel plates 52A and 52B having an input face 53A and output face 53B, a multilayer flexible lead assembly 54 and hardware 56 to secure the MCPs to the lead assembly. The flexible lead assembly 54 shown in the plan view of FIG. 2 is an integrated multilayer laminated structure formed with a detector end 58, a high voltage connector end 60 and an intermediate lead portion 62. The invention is designed to operate in high-vacuum and all components are high-vacuum compatible.

Detailed Description Paragraph Right (4):
In the MCP-based detector 50, the stack 51 of microchannel plates 52A and 52B (MCPs) is sandwiched between the high voltage input electrode and high voltage output electrode layers 64 and 66 and the anode layer 68 is positioned adjacent the output electrode layer 66 facing the output face 53B of the stack 51, as seen in FIG. 5. The electrode layers 64 and 66, anode 68 and the MCP stack 51 at detector end 58 of the flexible lead assembly 54 are held together with the mechanical hardware 56 which comprises an annular ring 90 at the input side and an apertured backing plate 92 adjacent the anode, as seen in FIG. 3. In the embodiment illustrated, the MCPs 52A and 52B are each formed with a corresponding central aperture 94 aligned along a common central axis 95 of the stack 51. The backing plate 92 is formed with a central tube 96 which extends into the aperture 87 in the anode layer 68 and the aperture 94 in the MCPs along the central axis 95. Alternatively, the MCPs and the backing plate may be formed without the central apertures or the tube.

CLAIMS:

1. An areal detector for both charged and neutral particles and energetic photons comprising: at least one microchannel plate (MCP) having a signal input face and signal output face; a flexible circuit having a detector end, an intermediate electrical lead portion with electrical shielding means and a connector end, and means for supporting said at least one MCP in said detector end of the flexible circuit; said flexible circuit including a pair of electrodes one each coupled to the respective signal input face and signal output face of said at least one MCP and at least one anode for collecting electron current signals from the signal output face of said at least one MCP.

15. A detector comprising: a microchannel plate (MCP) having electrically conductive input and output faces and an integrated multilayer flexible circuit having a detector end, a connector end and intermediate lead portion with electrical shielding means, said flexible circuit including an electrode layer for each face of the MCP and at least one anode for receiving signals from the output face of the MCP.

22. A lead assembly for a microchannel plate (MCP)-based detector comprising an integrated multilayer flexible circuit having a detector end, a connector end and intermediate lead portion, said flexible circuit including an electrode layer for each face of the MCP and at least one anode for receiving signals from the output face of the MCP.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw. Desc | Image

25. Document ID: US 5376252 A

L19: Entry 25 of 26 File: USPT Dec 27, 1994

US-PAT-NO: 5376252
DOCUMENT-IDENTIFIER: US 5376252 A

TITLE: Microfluidic structure and process for its manufacture
L19: Entry 25 of 26 File: USPT Dec 27, 1994

US-PAT-NO: 5376252
DOCUMENT-IDENTIFIER: US 5376252 A

TITLE: Microfluidic structure and process for its manufacture

DATE-ISSUED: December 27, 1994

US-CL-CURRENT: 204/603; 204/604, 210/198.2, 210/656, 422/947, 73/23.39, 73/61.53

APPL-NO: 7/ 946332
DATE FILED: November 10, 1992

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
SE	9001699.9	May 10, 1990

L19: Entry 25 of 26 File: USPT Dec 27, 1994

DOCUMENT-IDENTIFIER: US 5376252 A
TITLE: Microfluidic structure and process for its manufacture

Abstract Paragraph Left (1):
The microfluidic structure comprises first and second substantially planar form-stable base layers and an intermediate spacing layer of elastic material, said spacing layer being recessed to define a microcavity or channel system with at least one of said first and second base layers. The structure is produced by moulding the spacing layer, optionally applied to or integral with a first base layer, against a planar mould, and the microcavity or channel system is completed by applying a second base layer, and optionally said first base layer, to the spacing layer.

Brief Summary Paragraph Right (1):
The present invention relates to an improved microfluidic structure which may find use in various fields of application such as various electrophoretic procedures, capillary chromatography, liquid distribution systems and the like, as well as to a process for the manufacture thereof.

Brief Summary Paragraph Right (6):
An object of the present invention is to provide a microfluidic structure suitable for capillary electrophoresis and which is devoid of the above disadvantages and thus is relatively cheap to produce, optionally permitting a disposable type product, may provide branched flow channels, may exhibit local surface characteristics, and provides great freedom in choice of material, e.g. as regards surface, optical and electric properties.

Brief Summary Paragraph Right (7):
Another object of the present invention is to provide a microfluidic structure which, in addition to capillary electrophoresis, is suitable for other applications such as capillary chromatography, procedures using micro reaction cavities, miniaturized liquid communication units etc.

Brief Summary Paragraph Right (8):
Still another object of the present invention is to provide a microfluidic structure in the form of a multi-storey construction having channels or cavities in several planes to thereby permit the build-up of complex channel or cavity geometries for analyses or reactions.

Brief Summary Paragraph Right (9):
Another object of the present invention is to provide a microfluidic structure which permits easy detection of substances in the flow system.

Brief Summary Paragraph Right (10):

A further object of the present invention is to provide a process for the manufacture of the above microfluidic structure.

Brief Summary Paragraph Right (11):
Thus, in one aspect the present invention relates to a microfluidic structure comprising first and second substantially planar base layers of a form-stable material, and an intermediate spacing layer of elastic material, said spacing layer being recessed to define a micro cavity or channel system with at least one of said first and second base layers.

Brief Summary Paragraph Right (12):
In another aspect the present invention provides a process for the manufacture of such a microfluidic structure, which process comprises the steps of providing a mould having a planar face with a relief pattern corresponding to the desired spacing layer geometry, including said liquid flow system, applying and moulding a spacing layer material against the mould surface, optionally together or integral with a superposed first base layer, removing the mould from the shaped spacing layer, applying a second base layer to the shaped surface of the spacing layer to complete the liquid flow system therewith, and, if not done previously, applying said first base layer to the opposite surface of the spacing layer.

Detailed Description Paragraph Right (1):
In its simplest form the microfluidic structure according to the present invention comprises two base layers between which an elastic spacing material, which is firmly attached to at least one of the base layers, forms a geometric micro structure defining the desired liquid flow system, e.g. one or more cavities or a labyrinth-like channel.

Detailed Description Paragraph Right (17):
For electrophoretic purposes the second base layer is advantageously provided with contact means, e.g. gold strips, at each end thereof, as well as detector means or at least provisions therefor. In such a case this second base layer is preferably made reusable, whereas the first base layer with attached spacing layer is of disposable type and separable from the second base layer such that after use the latter may readily be provided with a new base layer/spacing layer assembly.

Detailed Description Paragraph Right (18):
As mentioned above the microfluidic structure of the invention may, of course, advantageously also be designed for other microfluidic purposes than electrophoresis. Among those are e.g. capillary chromatography, micro-reaction cavity procedures, miniaturized liquid communication units, biosensor flow cells, etc. Reaction cavities constructed in accordance with the invention may, for example, be used for various forms of solid phase synthesis, such as peptide or oligonucleotide synthesis, PCR, DNA-solid phase sequencing reactions, just to mention a few.

Detailed Description Paragraph Right (32):
In the electrophoretic plate shown in FIGS. 1 and 5 the smaller base layer 2, 2a with attached spacing layer 3, which advantageously is of disposable type, may easily be torn off from the larger base layer 1 provided with detector means 7, whereupon a new base layer/spacing layer assembly 2, 3 may be applied to the base layer 1 which is the more expensive one of the two components.

CLAIMS:

1. A microfluidic structure, comprising:

first and second substantially planar form-stable base layers; and

a first intermediate spacing layer of elastic material, said first spacing layer being recessed to define a microcavity or channel system with at least one of said first and second base layers, said first spacing layer and at least one of said first and second base layers being made of the same material.

12. A process of producing a microfluidic structure, comprising the steps of:

(i) providing a planar mold surface having a relief pattern corresponding to a desired spacing layer geometry,

(ii) molding a spacing layer of elastic material against said planar mold surface, and

(iii) after removal from the mold, applying first and second substantially planar form-stable base layers to opposite sides of the spacing layer such that a channel or microcavity system is defined by the spacing layer with at least one of said first and second base layers.

14. A process of producing a microfluidic structure comprising the steps of:

(a) providing a planar mold surface having a relief pattern corresponding to a desired spacing layer geometry,

(b) molding a spacing layer of elastic material against said planar mold surface, the spacing layer being attached to or integral with a first substantially planar form-stable base layer, and

(c) after removal from the mold, applying a second substantially planar form-stable base layer to the opposite side of the spacing layer, such that a channel or microcavity system is defined by the spacing layer with at least one of said first and second base layers.

18. A process of producing a microfluidic structure comprising the steps of:

a) providing a planar mold having a relief pattern corresponding to a desired spacing layer geometry;

b) applying a first base layer against the planar mold;

c) injecting a cross-linkable polymer liquid or thermoplastic polymer melt into a cavity defined between a surface of the planar mold and the base layer (2);

d) stabilizing said injected polymer by cross-linking or temperature reduction;

e) removing the base layer and spacing layer from the planar mold; and

f) applying a second base layer to the spacing layer of said structure.

23. A process of producing a microfluidic structure comprising the steps of:

a) providing a planar mold having a relief pattern corresponding to a desired spacing layer geometry;

b) applying a cross-linkable or thermoplastic spacing layer material, against the planar mold and pressing the spacing layer and the planar mold together;

c) stabilizing the spacing layer formed by cross-linking or temperature reduction;

d) removing the spacing layer from the mold; and

e) applying first and second base layers to opposite sides of the spacing layer.

25. A process of producing a microfluidic structure comprising the steps:

a) providing a planar mold having a relief pattern corresponding to a desired spacing layer geometry;

b) applying a cross-linkable or thermoplastic spacing layer material supported by or integral with a first base layer against the planar mold and pressing the spacing layer and the planar mold together;

c) stabilizing the spacing layer formed by cross-linking or temperature reduction;

d) removing the spacing layer and the first base layer from the mold; and

e) applying a second base layer to the spacing layer.

26. Document ID: US 5099128 A

L19: Entry 26 of 26 File: USPT Mar 24, 1992

US-PAT-NO: 5099128
DOCUMENT-IDENTIFIER: US 5099128 A

TITLE: High resolution position sensitive detector

L19: Entry 26 of 26 File: USPT Mar 24, 1992

US-PAT-NO: 5099128
DOCUMENT-IDENTIFIER: US 5099128 A

TITLE: High resolution position sensitive detector

DATE-ISSUED: March 24, 1992

US-CL-CURRENT: 250/370.11; 250/363.06, 250/363.1, 250/370.09

APPL-NO: 7/ 325137
DATE FILED: March 17, 1989

L19: Entry 26 of 26 File: USPT Mar 24, 1992

DOCUMENT-IDENTIFIER: US 5099128 A
TITLE: High resolution position sensitive detector

Abstract Paragraph Left (1):
A high spatial resolution gamma ray detector employs layers of scintillators, microchannel photomultipliers and sensors arrays of anodes to provide real time imaging of nuclear sources. Specific embodiments include a camera for detecting nuclear weapons within opaque containers and a device for discriminating exoatmospheric reentry vehicles from decoys.

Brief Summary Paragraph Right (5):
It is a further object of the present invention to provide such a detector as a structure comprising a scintillator, a microchannel plate and a layer of anodes that respond to impinging radiation by changing the state of the anodes, together with electronics to read out the location of the anodes whose state has changed.

Drawing Description Paragraph Right (6):
FIG. 4a is a side view of the microchannel arrays of the present invention and their relation to the scintillator crystal and anode arrays.

Drawing Description Paragraph Right (7):
FIG. 4b is a top view of a microchannel array of FIG. 4a.

Drawing Description Paragraph Right (11):
FIG. 6a is a cut-away view of a microchannel plate.

Drawing Description Paragraph Right (12):
FIG. 6b is a blow-up of an element of the microchannel plate of the present invention.

Detailed Description Paragraph Right (8):
The high resolution detector 11 uses an advanced focal plane array (FPA) technology, and a stacked scintillator crystal design. It is shown in detail in FIGS. 3a-6b. As shown in FIG. 3a, several subsensor assemblies 13 are stacked to form a detector. Each subsensor assembly 13 is a multi-layered, solid state, radiation hard structure. An individual subsensor assembly is depicted in FIG. 3b. It comprises a layered structure

including a thin scintillator crystal slab 15 typically NaI (TI) or Bismuth Germanate crystals, a microchannel plate amplifier array 16, a detector array of anodes 18, on a silicon-sapphire substrate 20, and a printed circuit board 21. The anodes can be made as small as necessary; the total scintillator thickness is maintained at a gamma-ray attenuation length (or more) while the highest resolution is achieved.

Detailed Description Paragraph Right (10):
The single multilayer sensors are stacked to obtain a high resolution, high efficiency, high energy particle measuring device. The inefficiency of a single layer due to the large particle range or inefficiency due to a thick scintillator is overcome. Stacking ordinary photomultiplier tubes is much less efficient because of their large size. The microchannel plate/anode combinations will only be 0.2 to 0.3 cm thick. This makes effective stacking possible.

Detailed Description Paragraph Right (12):
The microchannel plate 16 of FIG. 3b is an array of small channel electron multipliers also shown in FIG. 6a used to amplify an electron beam containing spatial information. Many such channels stand over a single anode. A typical diameter of a single channel is 50.times.10.sup.-4 cm. Each cylindrical channel 27 functions as a conventional photomultiplier tube. Each channel is a glass tube with its inner surface made semiconducting and will emit secondary electrons when bombarded with primary electrons accelerated in an electric field. Electrons enter the microchannel (See FIG. 6b) and strike the wall to produce secondary electrons which are accelerated axially along the channel by an electric field. The transverse energy of emission causes the electrons to cross the channel wall and produce more secondary electrons. This process is repeated until a large number of electrons emerge from the microchannel plate.

Detailed Description Paragraph Right (13):
Under ordinary room temperature conditions thermal noise generated in the detectors could overwhelm the scintillator photon signal. Reduced temperature operation is avoided in the present invention by having the microchannel plates amplify the scintillation photons so the detector signals are well above the room temperature detector noise.

Detailed Description Paragraph Right (14):
In operation radiation strikes a scintillator and produces photons that in turn produce electrons in the microchannel plate. These electrons neutralize a positive charge on the anode elements. In the unit cell associated with each of the anodes in FIG. 4b is a readout capacitor. The charge state of the anode is transferred to the capacitor and the anode is reset to its original charge state. The image of the nuclear source is thus contained in information of the location of the capacitors that contain information of an anode that received electrons from the microchannel plate.

Detailed Description Paragraph Right (24):
The readout chip employs the direct readout approach which incorporates a switched capacitor per anode/readout. Unlike conventional readout circuits which require external address polling of each and every unit cell in the array, the ARO design provides the address of the unit cell in the sensor array to be serviced by the Sensor Board Electronics (SBE). Only the unit cells with valid data are serviced, allowing for a very large sensor array coupled with high data repetition rates. This approach is made possible by the high gains for the microchannel plates amplifying the sensor signal and allowing the unit cell to toggle logic identifying valid data.

Detailed Description Paragraph Right (26):
The high resolution detector sensor employs a source follower per anode/readout to achieve low noise and wide dynamic range. During circuit initialization, the reset MOSFET (Min) 57 charges the sense capacitor 59 to a predetermined value (Vrs). FIG. 13 is a timing diagram of unit cell operation. The sense capacitor 59 is discharged by the anode when electrons from the microchannel plates strike the anode. The discharge capacitor turns on transistor (Mtrig) 61 generating a logical high state flagging the address polling logic to stop and service this unit cell. The internal address polling logic in the ARO chip is functionally very similar to a controlled ring oscillator. The address polling logic is initialized with a (.phi.nc) of the next unit cell. In this way a serpentine polling chain is created.

Detailed Description Paragraph Right (36):
The sensor employs a source follower per anode readout and multiplexer circuitry to achieve low noise and wide dynamic range. During circuit initialization, the reset MOSFET (Mrst) charges the sense capacitors (1 through 100) to a predetermined value

(Vrst) (FIG. 13 shows the preferred unit cell timing diagram.) This is accomplished by setting the 100 bit shift register to the on state by clocking (.phi.set) allowing all sense capacitors to be reset as indicated above. During this time all time stamp capacitors are also initialized to a predetermined value. When the sensor is activated (Mrst) is turned off and .phi.int is pulsed (10 ns) to initialize all unit cell logic. Initialization pulse (.phi.int) sets all logic in the shift register to the off state except for bit #1 which is on. The time stamp reference voltage (.phi.time) is slowly ramped up in time during data acquisition. The sense capacitor selected is discharged by electrons from the microchannel plates reacting to a gamma hit in the sodium iodide crystals. The sense capacitor discharge causes the shift register to be clocked (bit position #1 shifted to bit position #2). This has the effect of deselecting the current sense capacitor (#1) and selecting the next sequential sense capacitor (#2). Time stamp capacitor (#1) is also deselected and time stamp capacitor (#2) is now selected. The time stamp voltage on this capacitor is directly related to time since it is ramping up in time. This process is repeated for all acquired data until the sensor is deactivated. Transistor (Mrst) will at deactivation time be turned on preventing any further data acquisition All acquired data is thus stored in the capacitors and must be read out. The initialization pulse (.phi.int) is activated to reset the shift registers in all unit cells in preparation for data readout. The desired row and column is selected allowing either data or its associated time stamp to appear at Vout depending on the state of (.phi.rdt).

Detailed Description Paragraph Right (39):
Although the predominant application is with x-rays and gamma-rays (25 KeV to 25 MeV) any radiation can be detected with the microchannel plate/anode technology of the present invention as long as it produces light in scintillatory crystals--which any charged particle will do--or electrons--in which case the microchannel plate does not require a photoelectric element.

CLAIMS:

1. A position sensitive high resolution detector, said detector comprising as layers

a scintillator,

a microchannel plate amplifier array optically coupled to said scintillator and comprising a plurality of microchannels, each microchannel having a diameter substantially less than the resolution of said detector, and comprising a photocathode and a surface adapted to emit secondary electrons when bombarded with primary electrons,

a layer comprising one or more sensor chips each adapted to receive electrons from said microchannel plate amplifier and comprising

a substrate, and

a sensor array of anodes on said substrate, each anode adapted to change state in response to the emission of electrons from adjoining channels of said microchannel plate amplifier,

said detector further comprising sensor electronics adapted to read out data indicative of the location of the anodes whose state has changed.

11. A position sensitive high resolution stacked detector, said stacked detector comprising a plurality of layers of subsensor assemblies each comprising as layers

a scintillator,

a microchannel plate amplifier array optically coupled to said scintillator and comprising a plurality of microchannels, each microchannel having a diameter less than the resolution of said detector, and comprising a photocathode and a surface adapted to emit secondary electrons when bombarded with primary electrons,

a layer comprising a plurality of sensor chips each adapted to receive electrons from said microchannel plate amplifier and comprising

a substrate, and

a sensor array of anodes on said substrate, each anode adapted to change state in

response to the emission of electrons from adjoining channels of said microchannel plate amplifier,

said detector further comprising sensor electronics adapted to read out data indicative of the location of the anodes whose state has changed, and

said scintillators having a total thickness of at least about the attenuation length for gamma-rays traversing said individual scintillators.

17. The position sensitive high resolution detector of claim 11 wherein said layers of subsensor assemblies are contained in a vacuum housing.

20. A high resolution gamma-ray camera for imaging a nuclear radiation source comprising

an aperture mask adapted to absorb or scatter gamma-rays not passing through apertures in said mask, and

a position sensitive high resolution stacked detector, said stacked detector comprising a plurality of layers of subsensor assemblies each comprising as layers

a scintillator,

a microchannel plate amplifier array optically coupled to said scintillator and comprising a plurality of microchannels, each microchannel having a diameter less than the resolution of said detector, and comprising a photocathode and a surface adapted to emit secondary electrons when bombarded with primary electrons,

a layer comprising a plurality of sensor chips each adapted to receive electrons from said microchannel plate amplifier and comprising

a substrate, and

a sensor array of anodes on said substrate, each anode adapted to change state in response to the emission of electrons from adjoining channels of said microchannel plate amplifier,

said detector further comprising sensor electronics adapted to read out data indicative of the location of the anodes whose state has changed, and

said scintillators having a total thickness of at least about the attenuation length for gamma-rays traversing said individual scintillators.

33. A method for imaging at high resolution a source of radiation capable of producing photons in a scintillator comprising

passing said source of radiation into a scintillator,

passing said photons into a portion of a microchannel plate amplifier comprising a plurality of microchannels each having a diameter substantially less than said resolution and thereby causing electrons to be emitted from said portion of microchannels,

receiving the electrons from the microchannel plate amplifier on a portion of a sensor array of anodes on a substrate, whereby the state of said anodes that receive the electrons is changed,

reading out data indicative of the location of the anodes whose state has changed and forming an image of the source from said data.

38. The method of producing a high resolution image of a nuclear radiation source within an object comprising

causing gamma radiation from said source to fall on an aperture mask and passing gamma-rays through apertures in said mask

passing said source of radiation into a stacked detector comprising a plurality of scintillators,

passing photons from each of said scintillators into a portion of a microchannel plate amplifier associated with each scintillator, each microchannel plate comprising a plurality of microchannels having a diameter substantially less than said resolution and thereby causing electrons to be emitted from said portions of said microchannels,

receiving the electrons from the respective microchannel plate amplifiers on a portion of a sensor array of anodes on a substrate associated with each scintillator, whereby the state of said anodes that receive the electrons is changed,

reading out data indicative of the location of the anodes whose state has changed and forming an image of the source from said data.

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L24	l17 not l19	94	L24
L23	l15 not l19	94	L23
L22	L21 and l12	26	L22
L21	electron adj transfer adj moiet$4	43	L21
L20	electro adj transfer adj moiet$4	0	L20
L19	L18 and l12	26	L19
L18	((assembl$6 or selfassembl$6) near2 (layer or monolayer)) same detect$4	236	L18
L17	l13 not l16	110	L17
L16	l13 not l15	10855	L16
L15	L14 and (204/$.ccls. or 422/$.ccls. or 435/$.ccls. or 436/$.ccls.)	110	L15
L14	L13 and l12	320	L14
L13	(assembl$6 or selfassembl$6) near2 (layer or monolayer)	10965	L13
L12	L11 or l10 or l9 or l8 or l7 or l6 or l5 or l3 or l2 or l1	16927	L12
L11	mu adj tas	22	L11
L10	(total or micrototal) adj analysis adj system	38	L10
L9	nanoscale or (nano adj scale)	679	L9
L8	mesoscale or (meso adj scale)	106	L8
L7	microscale or (micro adj scale)	1529	L7
L6	microfluidic or (micro adj fluidic)	1112	L6
L5	microanaly$6 or (micro adj analy$6)	5672	L5
L4	microfabricat$6 or (micro adj fabricat$6)	2840	L4
L3	microconduit or (micro adj conduit)	34	L3
L2	microchannel or (micro adj channel)	4036	L2
L1	microchip or (micro adj chip)	4773	L1

END OF SEARCH HISTORY

WEST

Number of documents to display is limited to 50 for TI,DATE,KWIC format

Generate Collection | Print

Search Results - Record(s) 1 through 50 of 94 returned.

1. Document ID: US 6387707 B1

L23: Entry 1 of 94 File: USPT May 14, 2002

US-PAT-NO: 6387707
DOCUMENT-IDENTIFIER: US 6387707 B1

TITLE: Array Cytometry

L23: Entry 1 of 94 File: USPT May 14, 2002

US-PAT-NO: 6387707
DOCUMENT-IDENTIFIER: US 6387707 B1

TITLE: Array Cytometry

DATE-ISSUED: May 14, 2002

US-CL-CURRENT: 436/164; 422/50, 422/57, 422/60, 422/63, 422/67, 422/68.1, 427/2.12, 427/2.13, 427/483, 427/59, 427/77, 435/4, 435/6, 435/7.1, 435/7.2, 435/7.21, 435/7.23, 435/7.92, 435/7.93, 435/7.94, 435/7.95, 436/519, 436/538, 436/806, 436/807

APPL-NO: 9/ 320274
DATE FILED: May 28, 1999

PARENT-CASE:

This application is a continuation-in-part application of application Ser. No. 09/171,550, filed on Oct. 26, 1998, now U.S. Pat. No. 6,251,691, corresponding to PCT International Application No. PCT/US97/08159, filed on Apr. 24, 1997, which in turn is based on U.S. Provisional Application Serial No. 60/016,642, filed on Apr. 25, 1996. Applicants hereby claim the priority of these prior applications pursuant to 35 U.S.C. .sctn..sctn.119 and 120. These prior plications are incorporated herein by reference.

L23: Entry 1 of 94 File: USPT May 14, 2002

DOCUMENT-IDENTIFIER: US 6387707 B1
TITLE: Array Cytometry

Detailed Description Paragraph Right (42):
Colloidal particulates have been previously employed in flat-panel display technology. The operating principle of these designs is based on electrophoretic motion of pigments in a colored fluid confined between two planar electrodes. In the OFF (dark) state, pigments are suspended in the fluid, and the color of the fluid defines the appearance of the display in that state. To attain the ON (bright) state, particles are assembled near the front (transparent) electrode under the action of an electric field. In this latter state, incident light is reflected by the layer of particles assembled near the electrode, and the display appears bright. Prototype displays employing small reflective particles in accordance with this design are known. However, these displays suffered from a number of serious problems including: electrochemical degradation and lack of colloidal stability as a result of prolonged exposure to the high DC electric fields required to achieve acceptable switching speeds; and non-uniformities introduced by particle migration in response to field gradients inherent in the design of the

addressing scheme.

Detailed Description Paragraph Right (77):
The present invention of forming heterogeneous panels requires the chemical attachment of target ligands to beads. Ligands may be coupled to beads "off-line" by a variety of well established coupling reactions. For present purposes, the bead identity must be chemically encoded so it may be determined as needed. Several methods of encoding, including binary encoding, of beads are available. For example, short oligonucleotides may serve the purpose of identifying a bead via their sequence which may be determined by microscale sequencing techniques. Alternatively, chemically inert molecular tags may be employed that are readily identified by standard analytical techniques.

Detailed Description Paragraph Right (101):
Several methods of encoding, or binary encoding, of beads are available. Two examples are as follows. First, beads may be labeled with short oligonucleotides such as the 17-mers typically employed in hybridization experiments. The sequence of such short probes may be determined by microscale sequencing techniques such as direct Maxam-Gilbert sequencing or mass spectrometry. This encoding scheme is suitable when the task calls for screening of libraries of nucleic acid ligands or oligopeptides. Second, members of a combinatorial library may be associated with chemically inert molecular tags. In contrast to the previous case, these tag molecules are not sequentially linked. Instead, the sequence of reaction steps is encoded by the formal assignment of a binary code to individual tag molecules and their mixtures that are attached to the bead in each successive reaction step. The tags are readily identified by standard analytical techniques such as gas chromatography. This general encoding strategy is currently employed in the synthesis of combinatorial libraries on colloidal beads.

Detailed Description Paragraph Right (128):
The integration of this novel methodology of cellular analysis with sample preparation (electric-field induced lysis of cells) along with the technology of optically programmable bead arrays as disclosed herein creates a novel platform that combines an "on-chip"format of quantitative molecular interaction analysis and cellular analysis with microfluidics and optical imaging into a novel, multi-purpose assay platform.

Detailed Description Paragraph Right (130):
Flow cytometry and its application to fluorescence-activated cell sorting rely on a serial mode of analysis that requires the capture of individual cells into droplets which are passed, one at a time, through a small observation window. During a short time, e.g., 1-10 .mu.s, all measurements on a given cell must be completed. For example, the simultaneous analysis of a small number of cell surface markers represents the state of the art in flow cytometry (Beavis and Pennline, "Detection of Cell-Surface Antigens Using Antibody-conjugated Fluorospheres", BioTechniques 21, 498-503 (1996), the contents of which are incorporated herein by reference). Flow cytometric analysis represents just the last step in an assay: the instrumentation does not lend itself to the integration of liquid handling and automation of bioanalytical assays. This is in significant contrast to the present invention which integrates the optical manipulation of bead arrays and cellular assembly technology with microfluidics and optical imaging into a miniaturized platform for quantitative molecular and cellular analysis.

Detailed Description Paragraph Right (133):
Cytometry according to the present invention subsumes the entire set of capabilities for cellular analysis illustrated above into a common platform which is miniaturized and integrated with microfluidics and optical imaging and compatible with quantitative bear array format of molecular interaction analysis whose capabilities may be used in "multiplexed" fluorescence immunoassays and DNA hybridization assays.

Detailed Description Paragraph Right (152):
Control of cell assembly and microfluidic pathway enables direct in situ screening of secreted cellular markers. This model is illustrated in FIG. 25. Cellular arrays are assembled in one compartment of a two-compartment liquid reactor and are exposed to candidate drugs; the response is measured by monitoring a panel of secreted markers such as cytokines. Cell secretion are collected and introduced into a second compartment where they are profiled based on the response of a pre-deposited bead array using the READ format. Such a two-compartment reactor may be operated in parallel for multiple drug screening or kinetic analysis.

Current US Original Classification (1):
436/164

Current US Cross Reference Classification (1):
422/50

Current US Cross Reference Classification (2):
422/57

Current US Cross Reference Classification (3):
422/60

Current US Cross Reference Classification (4):
422/63

Current US Cross Reference Classification (5):
422/67

Current US Cross Reference Classification (6):
422/68.1

Current US Cross Reference Classification (12):
435/4

Current US Cross Reference Classification (13):
435/6

Current US Cross Reference Classification (14):
435/7.1

Current US Cross Reference Classification (15):
435/7.2

Current US Cross Reference Classification (16):
435/7.21

Current US Cross Reference Classification (17):
435/7.23

Current US Cross Reference Classification (18):
435/7.92

Current US Cross Reference Classification (19):
435/7.93

Current US Cross Reference Classification (20):
435/7.94

Current US Cross Reference Classification (21):
435/7.95

Current US Cross Reference Classification (22):
436/519

Current US Cross Reference Classification (23):
436/538

Current US Cross Reference Classification (24):
436/806

Current US Cross Reference Classification (25):
436/807

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

2. Document ID: US 6387631 B1

L23: Entry 2 of 94 File: USPT May 14, 2002

US-PAT-NO: 6387631
DOCUMENT-IDENTIFIER: US 6387631 B1

TITLE: Polymer coated surfaces for microarray applications

L23: Entry 2 of 94 File: USPT May 14, 2002

US-PAT-NO: 6387631
DOCUMENT-IDENTIFIER: US 6387631 B1

TITLE: Polymer coated surfaces for microarray applications

DATE-ISSUED: May 14, 2002

US-CL-CURRENT: 435/6; 422/68.1, 435/287.2, 435/287.9, 435/288.3, 435/4, 435/7.1, 530/300, 530/387.1, 530/388.1, 536/23.1

APPL-NO: 9/775319
DATE FILED: February 1, 2001

PARENT-CASE:

This application is a Continuation of application Ser. No. 09/532,419, filed Mar. 22, 2000.

L23: Entry 2 of 94 File: USPT May 14, 2002

DOCUMENT-IDENTIFIER: US 6387631 B1
TITLE: Polymer coated surfaces for microarray applications

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
422/68.1

Current US Cross Reference Classification (2):
435/287.2

Current US Cross Reference Classification (3):
435/287.9

Current US Cross Reference Classification (4):
435/288.3

Current US Cross Reference Classification (5):
435/4

Current US Cross Reference Classification (6):
435/7.1

Other Reference Publication (4):
Chrisey, L.A. et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nuc. Acids Res., 24(15): 3031-3039 (1996).

Other Reference Publication (6):
Beier, M. and J.D. Hoheisel, "Versatile derivatisation of solid support media for convalent bonding on DNA-microchips", Nuc. Acids Res., 27 (9): 1970-1977 (1999).

☒ 3. Document ID: US 6387614 B1

L23: Entry 3 of 94 File: USPT May 14, 2002

US-PAT-NO: 6387614
DOCUMENT-IDENTIFIER: US 6387614 B1

TITLE: Methods for using redox liposome biosensors

L23: Entry 3 of 94 File: USPT May 14, 2002

US-PAT-NO: 6387614
DOCUMENT-IDENTIFIER: US 6387614 B1

TITLE: Methods for using redox liposome biosensors

DATE-ISSUED: May 14, 2002

US-CL-CURRENT: 435/4; 435/5, 435/6, 435/7.1, 435/7.2, 435/7.21, 435/7.31, 435/7.32, 435/7.37, 436/149, 436/151, 436/501 , 436/518, 436/801, 436/806, 436/904

APPL-NO: 9/ 608788
DATE FILED: June 30, 2000

PARENT-CASE:

This application claims benefit under 35 U.S.C. .sctn.120 of provisional patent U.S. Ser. No. 60/142,861, filed on Jul. 7, 1999 which is herein incorporated by reference in its entirety for all purposes.

L23: Entry 3 of 94 File: USPT May 14, 2002

DOCUMENT-IDENTIFIER: US 6387614 B1
TITLE: Methods for using redox liposome biosensors

Detailed Description Paragraph Right (3):
LT toxin is a protein with a molecular weight of 82 kD, consisting of one A subunit (a translocation domain) and five identical B subunits (binding domains). The B subunits bind specifically to cell receptor ganglioside GM1, a glycosphingolipid localized on the cell surface of neurons and intestinal cells. As illustrated in FIG. 1, GM1 contains a carbohydrate recognition group and a hydrophobic ceramide tail, which allows it to be anchored into the cell membrane. Supramolecular assemblies such as monolayers and bilayer vesicles have proven to be an effective method for incorporating GM1 into the desired matrix for characterization and biosensing. During the development of the present invention, diacetylenic lipids derivatized with glycine headgroup (GLY-PDA) for making bilayer vesicles to host GM1 (FIG. 1, compound 1) were used.

Detailed Description Paragraph Right (55):
As used herein, the terms "organic matrix" and "biological matrix" refer to collections of organic molecules that are assembled into a larger multi-molecular structure. Such structures can include, but are not limited to, films, monolayers, and bilayers. As used herein, the term "organic monolayer" refers to a thin film comprised of a single layer of carbon-based molecules. In one embodiment, such monolayers can be comprised of polar molecules whereby the hydrophobic ends all line up at one side of the monolayer. The term "monolayer assemblies" refers to structures comprised of monolayers. The term "organic polymetric matrix" refers to organic matrices whereby some or all of the molecular constituents of the matrix are polymerized.

Detailed Description Paragraph Right (117):
Electrochemical characterization of the gel film was carried out by cyclic voltammetry

using Fe(CN).sub.6.sup.4-. The results showed that a great portion of current was suppressed, as compared to that on the bare electrode. However, a small portion of redox current for Fe(CN).sub.6.sup.4- was readily obtained. As the peak separation in CV curves was found to be comparable with that on a bare electrode, this suggests the presence of free electrode surface available for redox reaction, presumably from gel cracks. Thus, an Environmental SEM (ESEM) was utilized in order to further characterize the gel thin film on the electrode. ESEM was considered to be advantageous over conventional SEM for this study, since it allows for surface study under much milder conditions. FIG. 6A shows the ESEM image of a sol gel thin film on glassy carbon. The result revealed the presence of microscale cracks on the gel film, occupying less than 1% of the total area. Given the fact that the current for redox liposomes observed on gel surface decreases only slightly as compared to that on the bare electrode, it is obvious that the large current of redox vesicles on the gel-coated electrode is not totally originating from the gel cracks.

Current US Original Classification (1):
435/4

Current US Cross Reference Classification (1):
435/5

Current US Cross Reference Classification (2):
435/6

Current US Cross Reference Classification (3):
435/7.1

Current US Cross Reference Classification (4):
435/7.2

Current US Cross Reference Classification (5):
435/7.21

Current US Cross Reference Classification (6):
435/7.31

Current US Cross Reference Classification (7):
435/7.32

Current US Cross Reference Classification (8):
435/7.37

Current US Cross Reference Classification (9):
436/149

Current US Cross Reference Classification (10):
436/151

Current US Cross Reference Classification (11):
436/501

Current US Cross Reference Classification (12):
436/518

Current US Cross Reference Classification (13):
436/801

Current US Cross Reference Classification (14):
436/806

Current US Cross Reference Classification (15):
436/904

4. Document ID: US 6379929 B1

L23: Entry 4 of 94 File: USPT Apr 30, 2002

US-PAT-NO: 6379929
DOCUMENT-IDENTIFIER: US 6379929 B1

TITLE: Chip-based isothermal amplification devices and methods

L23: Entry 4 of 94 File: USPT Apr 30, 2002

US-PAT-NO: 6379929
DOCUMENT-IDENTIFIER: US 6379929 B1

TITLE: Chip-based isothermal amplification devices and methods

DATE-ISSUED: April 30, 2002

US-CL-CURRENT: 435/91.2; 435/91.1, 436/501

APPL-NO: 8/ 974738
DATE FILED: November 19, 1997

PARENT-CASE:

The present application claims the priority of co-pending U.S. Provisional Patent Application Ser. No. 60/031,590, filed Nov. 20, 1996, the entire disclosure of which is incorporated herein by reference without disclaimer. The government owns rights in the present invention pursuant to grant number R01-HG01044 from the National Institutes of Health.

L23: Entry 4 of 94 File: USPT Apr 30, 2002

DOCUMENT-IDENTIFIER: US 6379929 B1
TITLE: Chip-based isothermal amplification devices and methods

Brief Summary Paragraph Right (10):
These characteristics have led to the proposal of silicon and glass as a candidate technology for the construction of high-throughput DNA analysis devices (Woolley and Mathies, 1994; Northrup et al., 1993; Effenhauser et al., 1994). As mechanical materials, both silicon and glass have well-known fabrication characteristics (Petersen, 1982). Microfabricated devices for biochemical and fluidic manipulation are undergoing development in many laboratories around the world (Ramsey et al., 1995; McIntyre 1996). Over the past 10 years, a number of microfluidic devices have been developed that allow the construction of miniaturized "chemical reactors."Individual components of the system such as pumps (Esashi et al., 1989; Zengerle et al., 1992; Matsumoto and Colgate, 1990; Folta et al., 1992); valves (Esashi et al., 1989, Ohnstein et al., 1990; Smits, 1990); fluid channels (Pfahler et al., 1990); chromatographic and liquid electrophoresis separation systems (Terry et al., 1979; Harrison et al., 1992b-g; Manz et al., 1991; Manz et al., 1992) are available. Although an objective of several research groups, complete silicon-fabricated nucleic acids analysis systems are still at the earliest stages of development.

Brief Summary Paragraph Right (43):
A surface (such as a channel surface) is "hydrophobic" when it displays advancing contact angles for water greater than approximately 70.degree.. In one embodiment, the treated channel surfaces of the present invention display advancing contact angles for water between approximately 90.degree. and approximately 130.degree.. In another embodiment, the treated microchannels have regions displaying advancing contact angles for water greater than approximately 130.degree..

Brief Summary Paragraph Right (91):
The provision of the sample to the microfabricated or micromachined devices or systems is not believed to be critical, so long as the samples are later capable of being conveyed along the appropriate channels. Sample sources include, but are not limited to, continuous streams of liquid as well as static sources (such as liquid in a

reservoir). In a preferred embodiment, the source of liquid microdroplets comprises liquid in a microchannel from which microdroplets of a discrete size are split off. As described above, in certain preferred embodiments, the reagents for use in the isothermal reaction will already be comprised within a pre-fabricated microdevice. In such embodiments, lyophilized reagents may be rendered active by contact with the nucleic acid-containing sample, or alternatively, they may be separately contacted with another fluid sample, such as a buffer.

Brief Summary Paragraph Right (101):
A preferred technique is the Strand Displacement Amplification (SDA). The SDA reaction may be conducted at a substantially constant temperature between about 37.degree. C. and about 42.degree. C., or at any other effective temperature, as exemplified herein by 52.degree. C. It was previously believed that the low temperature requirement for SDA would prevent its use in connection with amplification on microchip devices. However, the inventors discovered that the potential problems of stagnant temperature gradients and reduced diffusion and sample mixing do not actually impact the efficiency of the SDA reaction in such microvolume embodiments.

Drawing Description Paragraph Right (2):
FIG. 2A and FIG. 2B. A two-part approach to construction of a silicon device of the present invention, and a silicon substrate comprising a plurality of devices. FIG. 2A shows one embodiment of a single microfluidic device. FIG. 2B shows one aspect of a silicon device comprising a plurality of microfluidic device modules.

Detailed Description Paragraph Right (3):
It was not previously known if the enzymatic activities required for such isothermal amplification reactions would be inhibited by interaction with the surfaces of silicon microfabricated analysis devices or by inhibitors present in the devices (e.g., residual chemicals from microfabrication). In addition, the change in surface-to-volume ratio which accompanies taking an enzymatic reaction developed in a test tube to the microchannel of a silicon microfabricated device may have unpredictable effects, as changes in the diffusion properties of the reactants in the channel may interfere with the amplification reaction. In particular for SDA, the interaction of the derivatized dNTPs with the microdevice environment, the effect of the environment on nicking activity by the restriction endonuclease and strand-displacing activity by the polymerase were not known. It is known that liquid movement in a closed channel, which is a convenient means for bringing components of the amplification reaction into contact, is affected by the contact angle of the liquid-gas-solid interface within the channel. Changes in the composition of the liquid in the channel change the surface tension and therefore the contact angle, affecting liquid movement. The contact angle is reduced and liquid movement is facilitated by more hydrophilic liquids such as the reaction buffers conventionally used in PCR.TM..

Detailed Description Paragraph Right (8):
In certain aspects, the present invention relates to movement of microdroplets through microchannels, and more particularly, compositions, devices and methods to control microdroplet size and movement. The present invention involves microfabrication of microscale devices and reactions in microscale devices, and in particular, movement of biological samples in microdroplets through microchannels to, for example, initiate biological reactions, particularly isothermal amplification of nucleic acids.

Detailed Description Paragraph Right (10):
The present invention contemplates microscale devices, comprising microdroplet transport channels, reaction regions (e.g., chambers), electrophoresis modules, and radiation detectors. In a preferred embodiment, these elements are microfabricated from silicon and glass substrates. The various components are linked (i.e., in liquid communication) using a surface-tension-gradient mechanism in which discrete droplets are differentially heated and propelled through etched channels. Electronic components are fabricated on the same substrate material, allowing sensors and controlling circuitry to be incorporated in the same device. Since all of the components are made using conventional photolithographic techniques, multi-component devices can be readily assembled into complex, integrated systems.

Detailed Description Paragraph Right (11):
Continuous flow liquid transport has been described using a microfluidic device developed with silicon (Pfahler et al., 1990). Pumps have also been described, using external forces to create flow, based on micromachining of silicon (Van Lintel et al., 1988). The present invention employs discrete droplet transport in silicon using internal forces or external forces (i.e., external forces created by pumps).

Detailed Description Paragraph Right (16):
FIG. 2A shows a two-part approach to construction. Microchannels (100) are made in the silicon substrate (200) and the structure is bonded to a glass substrate (300). The two-part channel construction technique requires alignment and bonding processes but is amenable to a variety of substrates and channel profiles. In other words, for manufacturing purposes, the two-part approach allows for customizing one piece (i.e., the silicon with channels and reaction formats) and bonding with a standardized (non-customized) second piece, e.g., containing standard electrical pads (400).

Detailed Description Paragraph Right (43):
The surface treatment of the channels may be done by immersing the open channel in organosilane or a self-assembled monolayer coating, with oxygen reactive ion etching removing the surface from unwanted areas. Heating elements, dielectric sensors, and connecting wires may be made from sputtered aluminum metal and conventional masking. The sequential activation of heating elements can be computer controlled through external circuitry, and a printed circuit board connector.

Detailed Description Paragraph Right (49):
A surface (such as a channel surface) is "hydrophobic" when it displays advancing contact angles for water greater than approximately seventy degrees. In one embodiment, the treated channel surfaces of the present invention display advancing contact angles for water between approximately ninety (90) and approximately one hundred and thirty (130) degrees. In another embodiment, the treated microchannels have regions displaying advancing contact angles for water greater than approximately one hundred and thirty (130) degrees.

Detailed Description Paragraph Right (57):
A 0.1 .mu.m layer of chromium metal is electronbeam deposited on the processed water. Photoresist PR 1827 is applied and spun at 2000 rpm for 30 sec. The resist is patterned (SAM mask) and developed. The exposed chromium metal is etched in chromium etchant to expose the silicon oxide and the photoresist is then stripped off. The samples are then cleaned in acetone, isopropyl alcohol and DI water for 10 min each, air dried and oven dried at 100.degree. C. for 5 min. The samples are then put in 1 wt % octadecyltrichlorosilane (OTS) solution in toluene for 15-30 min. OTS deposits on the samples as a self assembled monolayer (SAM). The samples are then rinsed in toluene, isopropyl alcohol and DI water for 5 min each, and then oven dried (100.degree. C., 5 min). Next, they are put in chromium etchant to remove the chromium layer below. The SAM on the chromium metal gets lifted off as a result of this. The samples were then rinsed in DI water and air dried, resulting in regions of intact hydrophobic regions on a hydrophilic oxide substrate. Heater elements and RTDs have also been fabricated on a quartz substrate. The fabrication steps are similar to that of the silicon processing steps.

Detailed Description Paragraph Right (59):
The mixing chamber consists of an enlarged portion of the microchannel structure, with one or more microchannels connected to the chamber. The mixing chamber is suspended on a thin silicon nitride diaphragm. This construction allows for excellent thermal isolation, as needed for low power heat cycling of the mixture. Construction of membrane suspended structures has been demonstrated (Mastrangelo et al., 1991). The heating is effected with a set of concentric resistors (heaters) that are placed on the periphery of the mixing chamber. This design, along with the high thermal conductivity of the liquid sample, makes the chamber temperature quite uniform. Along with the heaters, temperature sensors (diodes) are constructed on the diaphragm to monitor the temperature of the mixture. The low mass construction of the chamber allows for rapid heating cycles. Temperature control may handle samples of variable volume and heat capacity. The chamber also contains a set of electrodes and heating elements to drive the mixture out of the chamber at the completion of the reaction.

Detailed Description Paragraph Right (60):
The present invention contemplates one or more gel electrophoresis modules as a component of the microscale device. Reducing the thickness of the electrophoresis channel may improve resolution. Thinner gels dissipate heat more readily and allow higher voltages to be used, with concomitant improvements in separation. The position and width of the electrophoresis detector are also critical to the ultimate resolution of the electrophoresis system. A micromachined electronic detector, such as a photodiode, placed in the underlying silicon substrate may be less than one micron from the gel matrix and can have a width of 5 microns or less. Since the gel length required for the resolution of two migrating bands is proportional to the resolution of the

detector, the incorporation of micron-width electronic detectors can reduce the total gel length required for standard genotyping by at least an order of magnitude.

Detailed Description Paragraph Right (80):
It has also been found empirically that the methods and devices of the present invention may be used with success when regions of the microchannel are treated with hydrophobic reagents to create hydrophobic regions. By using defined, hydrophobic regions at definite locations in microchannels and using a pressure source, one can split off precise nanoliter volume liquid drops (i.e., microdroplets) and control the motion of those drops though the microchannels.

Detailed Description Paragraph Right (87):
The present invention contemplates methods, compositions and devices for the creation of microdroplets of discrete (ie., controlled and predetermined) size. The present invention contemplates the use of selective hydrophobic coatings to develop a liquid-sample injection and motion system that does not require the use of valves. In one embodiment, the present invention contemplates a method of lift-off to pattern hydrophobic and hydrophilic regions on glass, quartz and silicon substrates, involving the deposition of a hydrophobic reagent (such as a self-assembled monolayer film of OTS) on a silicon oxide surface pattered by a metal layer and subsequent removal of the metal to give hydrophobic patterns. Other substrates such as plastics may also be used after depositing a think film of silicon oxide or spin-on-glass.

Detailed Description Paragraph Right (96):
The present invention contemplates microscale devices, comprising microdroplet transport channels having hydrophilic and hydrophobic regions, reaction chambers, gas-intake pathways and vents, electrophoresis modules, and detectors, including but not limited to radiation detectors. In some embodiments, the devices further comprise air chambers to internally generate air pressure to split and move microdroplets (i.e., "on-chip" pressure generation).

Detailed Description Paragraph Right (117):
FIG. 2B shows a physical layout of a constructed chip. It consists of a two wafer bonded structure. One of the wafers is made of silicon and the other is glass. In the glass wafer, two levels of thin-film aluminum are patterned to make electrodes, interconnects, and heaters for the driven mechanisms. On the silicon wafer, the chip is patterned with microchannels and sample inlets and outlets. The two wafers are bonded together to complete the system. The sample is moved inside the channel using a linear array of electrical devices.

Detailed Description Paragraph Right (118):
Three propulsion mechanisms are contemplated other than the thermal surface tension method for fluid propulsion chips. Microchannels with electrowetting (Beni and Tenan, 1981; Matsumoto and Colgate, 1990; Washizu, 1992), dielectrophoretic, and thermal gradient (Van Lintel, 1988; Pohl, 1978) drives have been fabricated. Briefly, electrowetting propulsion relies on charge-induced change in the hydrophobicity (wetting) characteristics of the channel wall. Induction of a current along the channel makes the wall more hydrophilic, drawing the liquid drop toward the activated electrode. Dielectrophoresis utilizes the difference in dielectric constant between water and air. A liquid drop will be preferentially draw in between the plates of a charged capacitor. Each chip is designed to move samples in the 5-50 nL range.

Detailed Description Paragraph Right (119):
Twenty-seven devices were fabricated from a single 100 mm diameter wafer. The chips are cut out of the wafer and bonded to a printed circuit (PC) board. The setup is constructed to control the signals to each microchannel heater or electrode using a computer for sample droplet formation, separation, and movement control. The complete fabrication process requires 5 lithographic steps and was completed in one week. Microchannels with thicknesses of 20, 50, 100, and 200 .mu.m deep and 500-1000 .mu.m width were patterned. Each of these was fabricated with 20, 50, or 150 electrodes along the microchannel length.

Detailed Description Paragraph Right (125):
A drop of solution is placed on the hydrophilic input reservoir to form a sessile drop. The reservoir is connected to the entrance of a microchannel that delivers the sample into the MIDAT device. A portion of the channel is then made hydrophilic by charging a set of electrodes. Once the required amount of liquid is drawn into the device, the region near the junction of the reservoir and the channel is made locally hydrophobic by turning off the most proximal electrode. Alternatively, a brief burst of heating at

the junction could vaporize a small quantity of the sample and break the continuity of the drop. In either configuration, no further in-flow of liquid occurs. The drop is then moved forward by electrowetting or thermal surface tension effects, as discussed previously. Replacement air is drawn in through a small hydrophobic-coated channel. The volume of the drop is fixed by the cross-sectional area of the channel and the distance between cleavage point and the leading drop edge. Sample volumes as low as 10.sup.-12 liters may be manipulated by this system.

Detailed Description Paragraph Right (151):
A number of template dependent processes are available to amplify nucleotide sequences present in a given template sample. It is not intended that the present invention be limited by the nature of the reactions carried out in the microscale device. Reactions include, but are not limited to, chemical and biological reactions. Biological reactions include, but are not limited to sequencing, restriction enzyme digests, RFLP, nucleic acid amplification, and gel electrophoresis. It is also not intended that the invention be limited by the particular purpose for carrying out the biological reactions. In one medical diagnostic application, it may be desirable to differentiate between a heterozygotic and homozygotic target and, in the latter case, specifying which homozygote is present. Where a given genetic locus might code for allele A or allele a, the assay allows for the differentiation of an AA from an Aa from an aa pair of alleles. In another medical diagnostic application, it may be desirable to simply detect the presence or absence of specific allelic variants of pathogens in a clinical sample. For example, different species or subspecies of bacteria may have different susceptibilities to antibiotics; rapid identification of the specific species or subspecies present aids diagnosis and allows initiation of appropriate treatment.

Detailed Description Paragraph Right (192):
Using a radiograph of a 55 cm long, 400 .mu.m thick polyacrylamide sequencing gel that was run for 2 h at 2000 V (58 W) gel, these equations may calculate whether the 360 volts in the 10 cm gel would be able to obtain 400 bp resolution. The mobility, .mu..sub.400, is given by (dL)/(Vt)=3.1.times.10.sup.-5 cm.sup.2 /Vs. Since the 399 and the 400 bp-length fragments are 0.03 cm apart (band 399 and 397 are 0.06 cm apart, therefore 399 and 400 are .apprxeq.0.06/2 cm apart), then .DELTA..mu., is ((.DELTA.d)L)/(Vt)=9.2.times.10.sup.-8 cm.sup.2 /Vs. D.sub.eff is more difficult to obtain. If the plot of the width of a bands vs, t.sup.1/2, D.sub.eff,ave may be found, using equation 11, from the slope of the straight line through the points. This was difficult to do for the 400 bp band but the plot of this information for the 133 bp long fragment may obtain an estimate of D.sub.eff,ave =7.times.10.sup.-8 cm.sup.2 /s. This value is significantly above the molecular diffusion coefficient of DNA in free solution (.about.10.sup.-9 cm.sup.2 /s) and probably represents both the dispersion caused by the gel matrix and the low resolution of the x-ray film (Lang and Coates, 1968). Note that this calculation assumes that the sample was applied in an infinitesimally small sample volume; the zero intercept on the plot indicates that this is essentially true. The microfluidic devices in the MIDAT system may be used to introduce the sample in a similar fashion as what is done on the large scale.

Detailed Description Paragraph Right (234):
The controlled movement and mixing of nanoliter drops in micron-scale channels has been demonstrated using a differential-heating propulsion mechanism Control circuitry may maintain uniform biochemical reaction conditions and to reproducibly measure and detect the location of individual drops. The individual micro fluidic components for DNA sequencing may maintain compatibility among the devices. A variety of photofabricated, integrated DNA analysis systems is contemplated.

Detailed Description Paragraph Right (284):
This example describes approaches to the problem of forming a moisture barrier over electrical elements of the microscale device. Initial prototypes employed 5000 angstroms of aluminum and covered it with PECVD SiO.sub.x. Upon testing, it was determined that the liquids were penetrating this later and destroying the aluminum heating elements.

Detailed Description Paragraph Right (316):
In this example, a low melting point solder was intended to be utilized in the test structure. Because a universally useful solder-sealed microvalve will be used in a gas phase microanalytical system, it is not desirable to use a high melting point (m.p.) solder (>200.degree. C.), which might affect the gas properties. In addition, a high m.p. solder may affect other components on the device, such as integrated circuits, and increase power consumption. As a result, low melting point solder is required. Bismuth-bearing solders have the lowest m.p.'s of 47-138.degree. C. However, when a

test structure was dipped into a pool of solder belonging to this group, all the metal layers dissolved into the solution of solder. Moreover, this solder was not selective in wetting the surface of the test structure.

Detailed Description Paragraph Left (3):
A. Microchannel Construction

Detailed Description Paragraph Left (15):
C. Characteristics of Micro-Scale Fluids

Detailed Description Paragraph Left (20):
D. Micro-Scale Fluid/Solute Parameters

Detailed Description Paragraph Center (2):
1. DESIGN OF MICROSCALE DEVICES FOR ISOTHERMAL AMPLIFICATION REACTIONS

Detailed Description Paragraph Type 0 (40):
Jacobson and Ramsey, "Microchip electrophoresis with sample stacking," Electrophoresis, 16:481-486, 1995.

Detailed Description Paragraph Type 0 (42):
Jacobson, Hergenroder, Koutny, Warmack, Ramsey, "Effects on injection schemes and column geometry on the performance of microchip electrophoresis devices," Anal. Chem., 66:1107-1113, 1994a.

Detailed Description Paragraph Type 0 (43):
Jacobson, Hergenroder, Koutny, Ramsey. "High-speed separations on a microchip," Anal. Chem., 66:1114-1118, 1994b.

Detailed Description Paragraph Type 0 (44):
Jacobson, Hergenroder, Koutny, Ramsey, "Open Channel Electrochromatography on a Microchip." Anal Chem. 66:2369-2373, 1994c.

Detailed Description Paragraph Type 0 (61):
Manz, Verpoorte, Raymond, Effenhauser, Burggraf, Widmer, ".mu.TAS: Miniaturized total chemical analysis," In: Micro-total analysis systems, 5-27, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1995.

Detailed Description Paragraph Type 0 (108):
Van den Berg, and Bergveld, In: MESA Monograph: Micro Total Analysis Systems, Kluwer Academic Publishers, Boston, 1995.

Current US Original Classification (1):
435/91.2

Current US Cross Reference Classification (1):
435/91.1

Current US Cross Reference Classification (2):
436/501

5. Document ID: US 6377721 B1

L23: Entry 5 of 94 File: USPT Apr 23, 2002

US-PAT-NO: 6377721
DOCUMENT-IDENTIFIER: US 6377721 B1

TITLE: Biosensor array comprising cell populations confined to microcavities

L23: Entry 5 of 94 File: USPT Apr 23, 2002

US-PAT-NO: 6377721
DOCUMENT-IDENTIFIER: US 6377721 B1

TITLE: Biosensor array comprising cell populations confined to microcavities

DATE-ISSUED: April 23, 2002

US-CL-CURRENT: 385/12; 385/115, 385/116, 385/117, 385/120, 385/14, 385/147, 385/901, 436/164, 436/172, 436/800, 436/805

APPL-NO: 9/ 260963
DATE FILED: March 2, 1999

L23: Entry 5 of 94 File: USPT Apr 23, 2002

DOCUMENT-IDENTIFIER: US 6377721 B1
TITLE: Biosensor array comprising cell populations confined to microcavities

Brief Summary Paragraph Right (2):
It is generally recognized that important technical advances in chemistry, biology and medicine benefit from the ability to perform microanalysis of samples in minute quantities. However, making analytical measurements on minute quantities has long been a challenge due to difficulties encountered with small volume sample handling, isolation of analytes, and micro-analysis of single-cell physiology.

Brief Summary Paragraph Right (4):
Clark, et al. [Anal. Chem. 69(2):259(1997)] has disclosed a method for fabricating picoliter microvials for electrochemical microanalysis using conventional photolithographic masking and photoresist techniques to transfer mold polystyrene microvials on silicon wafer templates. These microvials typically exhibit non-uniformity in size and shape due to the difficulty in controlling the resist etching of the molding surface and the transfer molding process.

Brief Summary Paragraph Right (14):
Regnier, et al., [Trends in Anal. Chem. 14(4):177(1995)] discloses an invasive, electrophoretically mediated, microanalysis method for single cell analysis. The method utilizes a tapered microinjector at the injection end of a capillary electrophoresis column to pierce an individual cell membrane and withdraw a sample of cytoplasm. The method measures cell contents, one cell at a time. The method is generally limited to the detection of easily oxidized species.

Current US Cross Reference Classification (8):
436/164

Current US Cross Reference Classification (9):
436/172

Current US Cross Reference Classification (10):
436/800

Current US Cross Reference Classification (11):
436/805

Other Reference Publication (32):
Mrksich,et al., "Controlling Cell Attachment of Contored Surfaces with Self-assemble Monolayers of Alkanethiolates on Gold," Proc. Natl. Acad. Sci. USA 93:10775-10778 (Oct.1996).

Other Reference Publication (59):
Regnier, et al., "Electrophoretically-mediated Microanalysis," Trends in Analytical Chemistry, 14(4);177-181 (1995).

6. Document ID: US 6376258 B2

L23: Entry 6 of 94 File: USPT Apr 23, 2002

US-PAT-NO: 6376258
DOCUMENT-IDENTIFIER: US 6376258 B2

TITLE: Resonant bio-assay device and test system for detecting molecular binding events

L23: Entry 6 of 94 File: USPT Apr 23, 2002

US-PAT-NO: 6376258
DOCUMENT-IDENTIFIER: US 6376258 B2

TITLE: Resonant bio-assay device and test system for detecting molecular binding events

DATE-ISSUED: April 23, 2002

US-CL-CURRENT: 436/518; 435/287.1, 435/287.2, 435/6, 435/7.1, 435/7.92, 436/149, 436/150, 436/151, 436/517, 436/524, 436/525, 436/805, 436/806

APPL-NO: 9/ 480846
DATE FILED: January 10, 2000

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This application is a continuation of U.S. application Ser. No. 09/365,578, filed Aug. 2, 1999 and which is a continuation-in-part of U.S. application Ser. No. 09/243,194, entitled "Method and Apparatus for Detecting Molecular Binding Events," filed Feb. 1, 1999 and U.S. application Ser. No. 09/243,196, filed Feb. 1, 1999, which claims the benefit of U.S. Provisional Application No. 60/073,445, filed Feb. 2, 1998, the disclosures of which are herein incorporated by reference.

L23: Entry 6 of 94 File: USPT Apr 23, 2002

DOCUMENT-IDENTIFIER: US 6376258 B2
TITLE: Resonant bio-assay device and test system for detecting molecular binding events

Detailed Description Paragraph Right (25):
As used herein, the "bio-assay system" refers to the bio-assay device as described above, in connection with the components necessary to electromagnetically probe and detect the bio-assay device. These components include, but are not limited to, the signal path(s), substrate(s), electronic devices such as signal generators, oscilloscopes, and vector analyzers necessary to probe to and detect signals from the bio-assay device, microchips and microprocessors which can probe and detect electromagnetic signals and analyze data, and the like.

Detailed Description Paragraph Right (46):
The chemistry of the system generally occurs within the bio-assay device, and in particular along the conductive layer (signal path in FIGS. 1A-1C). The conductive layer is fabricated from materials and having a morphology which is conducive to support the propagation of the high frequency test signal. The conductive surface is constructed from materials exhibiting appropriate conductivity over the desired test frequency range as well as possessing good molecular binding qualities as described above. Such materials include, but are not limited to gold, indium tin oxide (ITO), copper, silver, zinc, tin, antimony, gallium, cadmium, chromium, manganese, cobalt, iridium, platinum, mercury, titanium, aluminum, lead, iron, tungsten, nickel, tantalum, rhenium, osmium, thallium or alloys thereof. The conductive layer may also be formed from semiconducting materials which may be either crystalline or amorphous in

structure, including chemically doped or pure carbon, silicon, germanium, gallium-arsenide, idium-gallium arsenide, or the like. The conductive material may also be formed from polymers especially those that are conductive such as polyacetylene, polythiophene and the like. The conductive layer may be thick or only several molecular layers in depth as the application requires. The conductive layer may be comprised of an evaporated thin metal layer or an epitaxial layer of gallium arsenide or other semiconductor materials rendered conductive through known semiconductor processing techniques. In addition, the conductive layer may be derivatized, the process by which is well known, e.g., see Kumar et al., "Patterned Self-Assembled Monolayer and Mesoscale Phenomena," Accounts of Cemical Research, 28:219-226 (1995).

Detailed Description Paragraph Right (94):
The system of detection formed through use of the bioassay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fab technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, New York, 1990.

Detailed Description Paragraph Right (227):
The invention described herein can also be used for many aspects of new drug development, from the initial screening process all the way though patient typing and therapeutic monitoring. In the initial stages of drug discovery, the invention can be used to facilitate target identification, validation, and high throughput screening (HTS). Target receptors can be the antiligand on the bio-assay device, and by characterizing the actions of known agonists, antagonists, or allosteric effectors, initial targets for the high throughput screening procedure can be rapidly identified and validated. In the HTS process, hundreds of thousands of compounds are tested to determine which of them can bind to the target. The invention described herein can be miniaturized, so that highly parallel screening platforms can be realized; platforms which are capable of screening hundreds or thousands of compounds simultaneously, and at the same time determining the effect of binding (e.g. agonist or antagonist), affinity, kinetics, etc. Additionally, such miniature systems require very small amounts of compound, thus greatly saving costs in purchasing said compounds from combinatorial libraries. The system of detection formed through use of the bio-assay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fabrication technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, New York, 1990.

Current US Original Classification (1):
436/518

Current US Cross Reference Classification (1):
435/287.1

Current US Cross Reference Classification (2):
435/287.2

Current US Cross Reference Classification (3):
435/6

Current US Cross Reference Classification (4):
435/7.1

Current US Cross Reference Classification (5):
435/7.92

Current US Cross Reference Classification (6):
436/149

Current US Cross Reference Classification (7):
436/150

Current US Cross Reference Classification (8):
436/151

Current US Cross Reference Classification (9):
436/517

Current US Cross Reference Classification (10):
436/524

Current US Cross Reference Classification (11):
436/525

Current US Cross Reference Classification (12):
436/805

Current US Cross Reference Classification (13):
436/806

Other Reference Publication (2):
Eggers et al. (1994). A microchip for quantitative detection of molecules utilizing luminescent and radioisotope recorder groups. BioTechniques. 17(3):516-523.*

7. Document ID: US 6368877 B1

L23: Entry 7 of 94 File: USPT Apr 9, 2002

US-PAT-NO: 6368877
DOCUMENT-IDENTIFIER: US 6368877 B1

TITLE: Self-assembling peptide surfaces for cell patterning and interactions

L23: Entry 7 of 94 File: USPT Apr 9, 2002

US-PAT-NO: 6368877
DOCUMENT-IDENTIFIER: US 6368877 B1

TITLE: Self-assembling peptide surfaces for cell patterning and interactions

DATE-ISSUED: April 9, 2002

US-CL-CURRENT: 436/527; 426/523, 426/524, 426/530, 426/531, 426/578, 427/2.11, 435/176, 435/177, 436/525, 530/326, 530/327, 530/328

APPL-NO: 8/ 882415
DATE FILED: June 25, 1997
L23: Entry 7 of 94 File: USPT Apr 9, 2002

DOCUMENT-IDENTIFIER: US 6368877 B1
TITLE: Self-assembling peptide surfaces for cell patterning and interactions

Abstract Paragraph Left (1):
This invention describes self assembled monolayers (SAMs) manufactured by imprinting reactive peptides onto solid supports. The invention further relates to methods of preparing and using these improved SAMs.

Brief Summary Paragraph Right (1):
Organic surfaces have been employed in numerous methods and systems, including as substrates for ELISA, cell and tissue culture. Self-assembled monolayers (SAMS) are a class of organic surfaces manufactured by imprinting a monolayer of organic compounds with reactive moieties onto a solid support under conditions wherein the compounds react with and bind to the solid support in a single ordered and patterned layer. See, Lopez, et al., "Convenient Methods for Patterning the Adhesion of Mammalian Cells to Surfaces Using Self-Assembled Monolayers of Alkanethiolates on Gold," J. Am. Chem. Soc., 115(13):5877-5878 (1993) and Mrksich and Whitesides, "Using Self-Assembled Monolayers to Understand the Interactions of Man-Made Surfaces with Proteins and Cells", Annu. Rev. Biophys. Biomol. Struct., 25:55-78 (1996). Molecular self-assembly is the spontaneous association of molecules under equilibrium conditions into stable, structurally well-defined order joined by non-covalent bonds. SAMs manufactured to date have linked chemical moieties to solid surfaces through long chain alkyl linkages. Examples of organic compounds which have been patterned on a solid support include alkanethiolates and alkylsiloxanes. The SAMs are manufactured employing a process termed "microcontact printing."

Brief Summary Paragraph Right (4):
Thus, the invention relates to a composition of matter comprising a solid support and a self-assembled monolayer of linear peptides wherein said peptides bound directly to said solid support through a terminal amino acid in a predetermined pattern. Preferably, the peptides comprise a terminal reactive group, a central linker and a presenting group. The invention also relates to the uses and applications of the SAMs described herein, as will be described in more detail below.

Brief Summary Paragraph Right (5):
The invention further relates to a method for manufacturing a SAM, or a composition of matter comprising a solid support and a self-assembled monolayer of linear peptides wherein said peptides bound directly to said solid support through a terminal amino acid in a predetermined pattern, comprising microcontact printing the reactive peptides onto the solid support and maintaining the peptides under conditions suitable for binding.

Detailed Description Paragraph Right (26):
As stated above, methods for the manufacture of SAMs are generally known in the art. U.S. Pat. Nos.: 5,620,850 and 5,512,131 the contents of which are incorporated herein by reference and PCT Published Application Nos.: W097/07429 and W096/29629 decribed suitable methods for manufacture. Additional examples include Deng,-Li, Milan Mrksich and George M. Whitesides, "Self-Assembled Monolayers of Alkanethiolates Presenting Tri(propylene sulfoxide) Groups Resist the Adsorption of Protein," J. Am. Chem. Soc., 118(21):5136-5137 (1996); Chen, Christopher S., Milan Mrksich, Sui Huang, George M. Whitesides, Donald E. Ingber, "Geometric Control of Cell Life and Death," Science, 276:1425-1428 (1997); Lopez, Gabriel P., Mark W. Albers, Stuart L. Schreiber, Reed Carroll, Ernest Peralta, and George M. Whitesides, "Convenient Methods for Patterning the Adhesion of Mammalian Cells to Surfaces Using Self-Assembled Monolayers of Alkanethiolates on Gold," J. Am. Chem. Soc., 115(13):5877-5878 (1993); Kumar, Amit, Nicholas L. Abbott, Enoch Kim, Hans A. Biebuyck, and George M. Whitesides, "Patterned Self-Assembled Monolayers and Meso-Scale Phenomena," Acc. Chem. Res., 28(5):219-226 (1995); DiMilla, Paul A., John P. Folkers, Hans A. Biebuyck, Ralph Harter, Gabriel P. Lopez, and George M. Whitesides, "Wetting and Protein Adsorption of Self-Assembled Monolayers of Alkanethiolates Supported on Transparent Films of Gold," J. Am. Chem. Soc., 116(5):2225-2226 (1994); Singhvi, Rahul, Amit Kumar, Gabriel P. Lopez, Gregory N. Stephanopoulos, Daniel I. C. Wang, George M. Whitesides, Donald E. Ingber, "Engineering

Cell Shape and Function," Science, 264:696-698 (1994); Mrksich, Milan and George M. Whitesides, "Using Self-Assembled Monolayers to Understand the Interactions of Man-Made Surfaces with Proteins and Cells," Annu. Rev. Biophys. Biomol. Struct., 25:55-78 (1996); Wilbur, James L., Amit Kumar, Enoch Kim, George M. Whitesides, "Microfabrication by Microcontact Printing of Self-Assembled Monolayers," Adv. Mater. 6(7/8):600-604 (1994); Xia, Younan, Enoch Kim, Milan Mrksich and George M. Whitesides, "Microcontact Printing of Alkanethiols on Copper and Its Application in Microfabrication," Chem. Mater. 8(3):601-603 (1996); Mrksich, Milan, Jocelyn R. Grunwell and George M. Whitesides, "Biospecific Adsorption of Carbonic Anhydrase to Self-Assembled Monolayers of Alkanethiolates that Present Benzenesulfonamide Groups on Gold," J. Am. Chem. Soc., 117(48):12009-12010 (1995); Jeon, Noo Li, Ralph G. Nuzzo, Younan Xia, Milan Mrksich, and George M. Whitesides, "Patterned Self-Assembled Monolayers Formed by Microcontact Printing Direct Selective Metalization by Chemical Vapor Deposition on Planar and Nonplanar Substrates," Langmuir, 11(8):3024-3026 (1995); Xia, Younan, Milan Mrksich, Enoch Kim and George M. Whitesides, "Microcontact Printing of Octadecylsiloxane on the Surface of Silicon Dioxide and Its Application in Microfabrication," J. Am. Chem. Soc., 117(37):9576-9577 (1995). The method is illustrated in FIGS. 1 and 2.

Current US Original Classification (1):
436/527

Current US Cross Reference Classification (7):
435/176

Current US Cross Reference Classification (8):
435/177

Current US Cross Reference Classification (9):
436/525

Other Reference Publication (6):
Knichel, M. et al., "Utilization of a self-assembled peptide monolayer for an impedimetric immunosensor," Sensors and Actuators B B28 (2) :85-94 (Aug. 1995).

Other Reference Publication (8):
Pale-Grosdemange, C. et al., "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo (ethylene glycol) of Structure HS(CH.sub.2).sub.11 (OCH.sub.2 CH.sub.2).sub.m OH on Gold," J. Am. Chem. Soc., 113(1) :12-20 (1991).

Other Reference Publication (10):
Prime, K.L. and Whitesides, G.M., "Adsorption of Proteins onto Surfaces Containing End-Attached Oligo (ethylene oxide) : A Model System Using Self-Assembled Monolayers," J. Am. Chem. Soc., 115(23):10714-10721 (1993).

Other Reference Publication (11):
Lopez, G.P., et al., "Fabrication and Imaging of Two-Dimensional Patterns of Proteins Adsorbed on Self-Assembled Monolayers by Scanning Electron Microscopy," J. Am. Chem. Soc., 115(23) :10774-10781 (1993).

Other Reference Publication (12):
Sigal, G.B., et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68:490-497 (1996).

Other Reference Publication (14):
Mrksich, M., et al., "Controlling cell attachment on contoured surfaces with self-assembled monolayers of alkanethiolates on gold," Proc. Natl. Acad. Sci. USA, 93:10775-10778 (1996).

Other Reference Publication (16):
Lopez et al., "Convenient Methods for Patterning the Adhesion of Mammalian Cells to Surfaces Using Self-Assembled Monolayers of Alkanethiolates on Gold," J. Am. Chem. Soc., 115(13) :5877-5878 (1993).

Other Reference Publication (17):
Mrksich and Whitesides, "Using Self-Assembled Monolayers to Understand the Interactions of Man-Made Surfaces with Proteins and Cells," Annu. Rev. Biophys. Biomol. Struct., 25:55-78 (1996).

Other Reference Publication (19):
Deng, L. et al., "Self-Assembled Monolayers of Alkanethiolates Presenting Tri(propylene sulfoxide) Groups Resist the Adsorption of Protein," J. Am. Chem. Soc., 118(21):5136-5137 (1996).

Other Reference Publication (21):
Kumar, A. et al., "Patterned Self-assembled Monolayers and Meso-Scale Phenomena," Acc. Chem. Res., 28(5) :219-226 (1995).

Other Reference Publication (22):
DiMilla, P.A. et al., "Wetting and Protein Adsorption of Self-Assembled Monolayers of Alkanethiolates Supported on Transparent Films of Gold," J. Am. Chem. Soc., 116(5) :2225-2226 (1994).

Other Reference Publication (24):
Wilbur, J.L., et al., "Microfabrication by Microcontact Printing of Self-Assembled Monolayers," Adv. Mater., 6(7/8) :600-604 (1994).

Other Reference Publication (26):
Mrksich, M., et al., "Biospecific Adsorption of Carbonic Anhydrase to Self-Assembled Monolayers of Alkanethiolates that Present Benzenesulfonamide Groups on Gold," J. Am. Chem. Soc., 117(48) : 12009-12010 (1995).

Other Reference Publication (27):
Jeon, N.L., et al., "Patterned Self-Assembled Monolayers Formed by Microcontact Printing Direct Selective Metalization by Chemical Vapor Deposition on Planar and Nonplanar Substrates," Langmuir, 11(8) :3024-3026 (1995).

CLAIMS:

1. A method for manufacturing a composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of linear peptides, wherein said peptides are bound to said solid support by a bond between the solid support and a terminal amino acid, said method comprising the steps:

(a) contacting an elastomeric stamp characterized by a relief of said pattern with a solution containing said linear peptide;

(b) contacting said stamp with a surface of said solid support under conditions suitable for the reaction between said linear peptide and said solid surface, wherein said linear peptide reacts with said solid support at points of contact between said stamp and said solid support, corresponding to the pattern; and

(c) removing said stamp.

2. A composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of two or more different linear peptides, wherein said peptides are bound to said solid support by a bond between the solid support and a terminal amino acid.

3. A composition of matter comprising: 1) a solid support; 2) and a printed pattern comprising a self-assembled monolayer of linear peptides,

wherein said peptides are bound to said solid support by a bond between the solid support and a terminal amino acid,

wherein said peptides comprise a terminal reactive group, a central linker and a presenting group selected from the group consisting of antigens, antibodies, antibody fragments, cellular adhesion motifs, high chain alkyls, hydrophobically blocked amino acids and ligands, and

wherein said peptides are extended beta strands.

4. A composition of matter comprising: 1) a solid support; 2) and a printed pattern comprising a self-assembled monolayer of linear peptides,

wherein said peptides are bound to said solid support by a bond between the solid support and a terminal amino acid,

wherein said peptides comprise a terminal reactive group, a central linker and a presenting group selected from the group consisting of antigens, antibodies, antibody fragments, cellular adhesion motifs, high chain alkyls, hydrophobically blocked amino acids and ligands,

wherein said terminal amino acid is selected from the group consisting of scrine, aspartic acid, glutamic acid and cysteine,

wherein said central linker comprises between 2 to 50 amino acids, and

wherein said central linker is selected from the group conisisting of a oligoglycine and oligoalanine.

7. A composition of matter comprising: 1) a solid support; and 2) a printed pattern comprising a self-assembled monolayer of two or more different linear peptides, wherein said peptides are bound to said solid support by a bond between the solid support and a terminal amino acid, the peptide further being characterized by the formula:

X--(CH.sub.2).sub.n --CH(NH.sub.2)CO(AA).sub.m --L

or

X--(CH.sub.2).sub.n --CH(COOH)NH(AA).sub.m --L

wherein

X is H, alkyl, alkoxy, alkylthio or dialkylamine, thiol, hydroxy, amino or carboxy;

each AA is independently the same or different and is a naturally-occurring or non-naturally-occurring amino acid;

L is a group which binds specifically or non-specifically to a target;

n is zero or an integer between 1 to 5; and

m is an integer of at least 2.

8. Document ID: US 6368795 B1

L23: Entry 8 of 94 File: USPT Apr 9, 2002

US-PAT-NO: 6368795
DOCUMENT-IDENTIFIER: US 6368795 B1

TITLE: Bio-assay device and test system for detecting molecular binding events

L23: Entry 8 of 94 File: USPT Apr 9, 2002

US-PAT-NO: 6368795
DOCUMENT-IDENTIFIER: US 6368795 B1

TITLE: Bio-assay device and test system for detecting molecular binding events

DATE-ISSUED: April 9, 2002

US-CL-CURRENT: 435/6; 204/400, 422/82.01, 422/82.02, 435/287.1, 435/287.2, 435/4, 435/7.1, 435/7.92, 436/149, 436/150, 436/151, 436/517, 436/518, 436/524, 436/525, 436/806

APPL-NO: 9/ 243194

DATE FILED: February 1, 1999

PARENT-CASE:

CROSS-REFERENCES TO RELATED APPLICATIONS
This application claims priority from a previously filed provisional application entitled: "The Detection of Molecular Binding Events on a Conductive Surface," Ser. No. 60/073,445, filed on Feb. 2, 1998, the contents of which are incorporated herein by reference.

L23: Entry 8 of 94 File: USPT Apr 9, 2002

DOCUMENT-IDENTIFIER: US 6368795 B1
TITLE: Bio-assay device and test system for detecting molecular binding events

Detailed Description Paragraph Right (41):
As used herein, the "bio-assay system" refers to the bio-assay device as described above, in connection with the components necessary to electromagnetically probe and detect the bio-assay device. These components include, but are not limited to, the signal path(s), substrate(s), electronic devices such as signal generators, oscilloscopes, and vector analyzers necessary to probe to and detect signals from the bio-assay device, microchips and microprocessors which can probe and detect electromagnetic signals and analyze data, and the like.

Detailed Description Paragraph Right (63):
The chemistry of the system generally occurs within the bio-assay device, and in particular along the conductive layer (interface transmission line in FIGS. 1A-1C). The conductive layer is fabricated from materials and having a morphology which is conducive to support the propagation of the high frequency test signal. The conductive surface is constructed from materials exhibiting appropriate conductivity over the desired test frequency range as well as possessing good molecular binding qualities as described above. Such materials include, but are not limited to gold, indium tin oxide (ITO), copper, silver, zinc, tin, antimony, gallium, cadmium, chromium, manganese, cobalt, iridium, platinum, mercury, titanium, aluminum, lead, iron, tungsten, nickel, tantalum, rhenium, osmium, thallium or alloys thereof The conductive layer may also be formed from semiconducting materials which may be either crystalline or amorphous in structure, including chemically doped or pure carbon, silicon, germanium, gallium-arsenide, idium-gallium arsenide, or the like. The conductive material may also be formed from polymers especially those that are conductive such as polyacetylene, polythiophene and the like. The conductive layer may be thick or only several molecular layers in depth as the application requires. The conductive layer may be comprised of an evaporated thin metal layer or an epitaxial layer of gallium arsenide or other semiconductor materials rendered conductive through known semiconductor processing techniques. In addition, the conductive layer may be derivatized, the process by which is well known, e.g., see Kumar et al., "Patterned Self-Assembled Monolayer and Mesoscale Phenomena," Accounts of Cemical Research, 28:219-226 (1995).

Detailed Description Paragraph Right (112):
The system of detection formed through use of the bioassay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fab technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, New York, 1990.

Detailed Description Paragraph Right (257):

The invention described herein can also be used for many aspects of new drug development, from the initial screening process all the way though patient typing and therapeutic monitoring. In the initial stages of drug discovery, the invention can be used to facilitate target identification, validation, and high throughput screening (HTS). Target receptors can be the antiligand on the bio-assay device, and by characterizing the actions of known agonists, antagonists, or allosteric effectors, initial targets for the high throughput screening procedure can be rapidly identified and validated. In the HTS process, hundreds of thousands of compounds are tested to determine which of them can bind to the target. The invention described herein can be miniaturized, so that highly parallel screening platforms can be realized; platforms which are capable of screening hundreds or thousands of compounds simultaneously, and at the same time determining the effect of binding (e.g. agonist or antagonist), affinity, kinetics, etc. Additionally, such miniature systems require very small amounts of compound, thus greatly saving costs in purchasing said compounds from combinatorial libraries. The system of detection formed through use of the bio-assay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fabrication technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, New York, 1990.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
204/400

Current US Cross Reference Classification (2):
422/82.01

Current US Cross Reference Classification (3):
422/82.02

Current US Cross Reference Classification (4):
435/287.1

Current US Cross Reference Classification (5):
435/287.2

Current US Cross Reference Classification (6):
435/4

Current US Cross Reference Classification (7):
435/7.1

Current US Cross Reference Classification (8):
435/7.92

Current US Cross Reference Classification (9):
436/149

Current US Cross Reference Classification (10):
436/150

Current US Cross Reference Classification (11):
436/151

Current US Cross Reference Classification (12):

436/517

Current US Cross Reference Classification (13):
436/518

Current US Cross Reference Classification (14):
436/524

Current US Cross Reference Classification (15):
436/525

Current US Cross Reference Classification (16):
436/806

Other Reference Publication (4):
Eggers et al. (1994). A microchip for quantitative detection of molecules utilizing luminescent and radioisotype reporter groups. BioTechniques. 17(3):516-523.*

☒ 9. Document ID: US 6361944 B1

L23: Entry 9 of 94 File: USPT Mar 26, 2002

US-PAT-NO: 6361944
DOCUMENT-IDENTIFIER: US 6361944 B1

TITLE: Nanoparticles having oligonucleotides attached thereto and uses therefor

L23: Entry 9 of 94 File: USPT Mar 26, 2002

US-PAT-NO: 6361944
DOCUMENT-IDENTIFIER: US 6361944 B1

TITLE: Nanoparticles having oligonucleotides attached thereto and uses therefor

DATE-ISSUED: March 26, 2002

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 536/22.1, 536/23.1, 536/24.3, 536/24.33

APPL-NO: 9/ 344667
DATE FILED: June 25, 1999

PARENT-CASE:

This application is a continuation-in-part of pending application Ser. No. 09/240,755, filed Jan. 29, 1999, which was a continuation-in-part of pending PCT application PCT/US97/12783, which was filed Jul. 21, 1997, which claimed benefit of provisional application No. 60/031,809, filed Jul. 29, 1996 now abandoned.

L23: Entry 9 of 94 File: USPT Mar 26, 2002

DOCUMENT-IDENTIFIER: US 6361944 B1
TITLE: Nanoparticles having oligonucleotides attached thereto and uses therefor

Drawing Description Paragraph Right (19):
FIGS. 19A-B: FIG. 19A is a graph of absorbance versus wavelength in nm showing changes in absorbance when gold nanoparticle-oligonucleotide conjugates assemble in multiple layers on a transparent substrate as illustrated in FIG. 13A. FIG. 19B is a graph of change in absorbance for the hybridized system referred to in FIG. 19A as the temperature is increased (melted).

Detailed Description Paragraph Right (123):
The nanomaterials and nanostructures that can be made by the nanofabrication method of the invention include nanoscale mechanical devices, separation membranes, bio-filters, and biochips. It is contemplated that the nanomaterials and nanostructures of the invention can be used as chemical sensors, in computers, for drug delivery, for protein engineering, and as templates for biosynthesis/nanostructure fabrication/directed assembly of other structures. See generally Seeman et al., New J. Chem., 17, 739 (1993) for other possible applications.

Detailed Description Paragraph Right (203):
DNA is the ideal synthon for programming the assembly of nanoscale building blocks into periodic two- and three-dimensional extended structures. The many attributes of DNA, which include ease of synthesis, extraordinary binding specificity, and virtually unlimited programmability by virtue of nucleotide sequence, can be exploited for the use of QD assembly.

Detailed Description Paragraph Right (221):
The results described in this example definitively establish that the immobilization of DNA onto QD surfaces has been achieved and that these particles can now be used in combination with DNA under hybridization conditions. Using DNA-functionalized QDs, the first DNA-directed formation of QD and mixed gold/QD nanoparticle structures has been demonstrated. The successful modification of semiconductor QDs with DNA has significant implications for materials research, and the door is now open for more extensive inquiries into the luminescent, electronic, and chemical properties of these unique building blocks as they are incorporated into new and functional multi-component nanostructures and nanoscale materials.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/91.1

Current US Cross Reference Classification (2):
435/91.2

10. Document ID: US 6355420 B1

L23: Entry 10 of 94 File: USPT Mar 12, 2002

US-PAT-NO: 6355420
DOCUMENT-IDENTIFIER: US 6355420 B1

TITLE: Methods and products for analyzing polymers

L23: Entry 10 of 94 File: USPT Mar 12, 2002

US-PAT-NO: 6355420
DOCUMENT-IDENTIFIER: US 6355420 B1

TITLE: Methods and products for analyzing polymers

DATE-ISSUED: March 12, 2002

US-CL-CURRENT: 435/6; 435/149, 435/287.1, 435/287.2, 435/94, 435/970, 435/973

APPL-NO: 9/ 134411
DATE FILED: August 13, 1998

PARENT-CASE:

RELATED APPLICATIONS
This patent application is a continuation of PCT/US98/03024, filed on Feb. 11, 1998, which claims the benefit of priority to U.S. Provisional Patent Application No. 60/037,921, filed on Feb. 12, 1997 and U.S. Provisional Patent Application No. 60/064,687, filed on Nov. 5, 1997.

L23: Entry 10 of 94 File: USPT Mar 12, 2002

DOCUMENT-IDENTIFIER: US 6355420 B1
TITLE: Methods and products for analyzing polymers

Brief Summary Paragraph Right (17):
In the sequencing by hybridization method, a target DNA is sequentially probed with a set of oligomers consisting of all the possible oligomer sequences. The sequence of the target DNA is generated with knowledge of the hybridization patterns between the oligomers and the target (Bains, 1991; Cantor et al., 1992; Drmanac et al., 1994). There are two possible methods of probing target DNA. The "Probe Up" method includes immobilizing the target DNA on a substrate and probing successively with a set of oligomers. "Probe Down" on the other hand requires that a set of oligomers be immobilized on a substrate and hybridized with the target DNA. With the advent of the "DNA chip," which applies microchip synthesis techniques to DNA probes, arrays of thousands of different DNA probes can be generated on a 1 cm.sup.2 area, making Probe Down methods more practical. Probe Up methods would require, for an 8-mer, 65,536 successive probes and washings, which would take an enormous amount of time. On the other hand, Probe Down hybridization generates data in a few seconds. With perfect hybridization, 65,536 octamer probes would determine a maximum of 170 bases. With 65,536 "mixed" 1 1-mers, 700 bases can be generated.

Brief Summary Paragraph Right (29):
Methods for preparing polymers for analysis are also claimed herein. The combination of the long read length and the novel preparation methods results in a much more stream-lined and efficient process. Lastly, the actual time taken to read a given number of units of a polymer is a million-fold more rapid than current methods because of the tremendous parallel amplification supplied by a novel apparatus also claimed herein, which is referred to as a nanochannel plate or a microchannel plate. The combination of all these factors translates into a method of polymer analysis including sequencing that will provide enormous advances in the field of molecular and cell biology.

Brief Summary Paragraph Right (103):
The agent in one embodiment is an electromagnetic radiation source and the electromagnetic radiation source is a light emissive compound. In another embodiment the channel is selected from the group consisting of is a microchannel and a nanochannel.

Brief Summary Paragraph Right (113):
In another embodiment the light emissive compounds or quenching compounds are covalently bonded at discrete locations close to channels in said wall material, said channels defining interaction stations. The channels preferably are microchannels. In a more preferred embodiment the channels are nanochannels. The light emissive compounds or quenching compounds can be covalently bonded to the wall material in a manner whereby the surfaces of the wall material defining the channel are free of the light emissive compounds and quenching compounds.

Brief Summary Paragraph Right (115):
In one embodiment the light is applied to only selected regions of a surface of the wall material defining the rim of the channel. In another embodiment the channel has a first end and a second end, the rim being at the first end, and wherein the light is applied to the second end, the light passing through the channel to contact the photoprotected chemical groups at the rim of said first end. The channels preferably are microchannels. In a more preferred embodiment the channels are nanochannels.

Brief Summary Paragraph Right (117):
In one embodiment the light is applied to only selected regions of a surface of the wall material defining the rim of the channel. In a preferred embodiment the photoprotective chemical group is attached to only selected regions of the surface of

the wall material defining the rim of the channel. In another embodiment the channel has a first end and a second end, the rim being at the first end, and wherein the light is applied to the second end, the light passing through the channel to contact the photoprotected chemical groups at the rim of said first end. The channels preferably are microchannels. In a more preferred embodiment the channels are nanochannels.

Brief Summary Paragraph Right (121):
In one embodiment the openings are defined by channels in the wall. Preferably the openings are defined by microchannels in the wall. More preferably the openings are defined by nanochannels in the wall. In one embodiment the plurality of openings is at least two. In a preferred embodiment the plurality is at least 50.

Brief Summary Paragraph Right (123):
According to another aspect of the invention an apparatus for detecting a signal is provided. The apparatus includes a housing defining a first buffer chamber and a second buffer chamber, a wall supported by the housing and separating the first and second buffer chambers, a plurality of channels defined by the wall and providing fluid communications between the first and second buffer chambers, and a sensor for distinguishing and collecting channel dependent signals. Preferably the channel is a microchannel. More preferably the channel is a nanochannel. In one embodiment the plurality of channels is at least two. In a preferred embodiment the plurality is at least 50. Preferably the signal is an optical signal.

Drawing Description Paragraph Right (16):
FIG. 12 shows an apparatus constructed to hold a nanochannel (or microchannel) plate which is capable of generating an electric field.

Detailed Description Paragraph Right (76):
An intensified CCDs (ICCDs) camera consists of a photocathode, microchannel plate (MCP), and a phosphor screen in addition to the CCD camera. Fluorescence light impinges on the photocathode, releasing photoelectrons into the MCP. The MCP is a secondary electron multiplier consisting of an array of millions of glass capillaries (channels) fused into the form of a thin disc. When photoelectrons are incident upon the channels, secondary electrons are produced. Passage of the electrons through the channels produces an amplification that is directly controlled as the gain of the instrument. Each channel of the MCP corresponds to a picture element. The output of the MCP is focused onto a phosphor screen where electrons exiting from the MCP strike. The optical image is reproduced on the phosphor screen and is captured by a CCD camera.

Detailed Description Paragraph Right (99):
A nanoscale piezoelectric scanning tip can be used to read the different units of the polymer based on physical contact of the different polymer units with the tip. Depending on the size and shape of the polymer unit, different piezoelectric signals are generated, creating a series of unit dependent changes. Labels on units are physically different than native units and can create a ready means for detection via a piezoelectric scanning tip. Upon contact of a polymer unit with the tip, the piezoelectric crystals change and give rise to a current which is outputted to a detection device. The amplitude and duration of the current created by the interaction of the polymer unit and the tip is characteristic of the polymer unit.

Detailed Description Paragraph Right (186):
A "channel" as used herein is a passageway through a medium through which a polymer can pass. The channel can have any dimensions as long as a polymer is capable of passing through it. For instance the channel may be an unbranched straight cylindrical channel or it may be a branched network of interconnected winding channels. Preferably the channel is a straight nanochannel or a microchannel. A "nanochannel" as used herein is a channel having dimensions on the order of nanometers. The average diameter of a nanochannel is between 1 nm and 999 run. A "microchannel" as used herein is a channel having dimensions on the order of micrometers. The average diameter of a microchannel is between 1 .mu.m and 1 mm. Preferred specifications and dimensions of channels useful according to the invention are set forth in detail below. In a preferred embodiment, the channel is fixed in the wall.

Detailed Description Paragraph Right (228):
Other nanoporous materials which have been described in the art include a nanochannel array glass with pore densities as high as 3.times.10.sup.10 pores per square centimeter (R. J. Tonucci, B. L. Justus, A. J. Campillo, C. E. Ford, Science 258, 783 (1992) and Pearson and Tonucci, Science, 270: 68 (1995)). Douglas et al. have shown that the nanoscopic pores in a protein derived from a bacterium can be used to transfer

an image of these pores to an underlying substrate (Douglas, et. Al., Science 257: 642 (1992)). Finally, Ozin has discussed a wide variety of nanoporous solids that can be used as template materials (Ozin, G. Adv. Mater. 4:612 (1992)). Nishizawa et. al., describe the production of metal nanotubule membranes having radii as small as 0.8 nm (Nishizawa et. al., Science 268:700 (1995), describing nanotubules formed by plating gold onto the walls of pores in a commercially available polycarbonate filtration membrane (Poretics) containing cylindrical nanopores of uniform radius (25 nm, 6.times.10.sup.8 pores per square centimeter) running through the complete thickness (6 .mu.m) of the membrane. "The thickness of the Au layers deposited on the pore walls can be controlled by varying the plating time. As a result, the inside radius of the Au nanotubules can be varied at will [as determined from measurements of gas (He) flux across the tubule-containing membrane.]" Berggren et. al., have demonstrated techniques for nanolithography using self-assembled monolayers and a beam of neutral inert gas. Berggren et. al., Science 269: 1255-1257 (1995).

Detailed Description Paragraph Right (286):
An example of an apparatus constructed to hold a nanochannel (or microchannel) plate (120) which is capable of generating an electric field is presented in FIG. 12. The electric field, created by electrodes (128, 130), is used to draw the DNA through the nanochannels. The exemplary nanochannel plate is immersed in a slightly viscous buffer solution which helps to slow the transit of the polymer through the nanochannel, so as to allow for a longer signal collection time per base. In addition, on either side of the plate are electrodes (128, 130) immersed in the buffer solution. The ensemble of nanochannel plate, buffer compartments (122), and electrodes are contained in an optical quality glass chamber suitable for image analysis and are positioned adjacent to a 60.times.1.4 NA oil objective (126).

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/149

Current US Cross Reference Classification (2):
435/287.1

Current US Cross Reference Classification (3):
435/287.2

Current US Cross Reference Classification (4):
435/94

Current US Cross Reference Classification (5):
435/970

Current US Cross Reference Classification (6):
435/973

CLAIMS:

116. The method of claim 52, wherein the channel is a microchannel.

117. The method of claim 49, wherein the channel is a microchannel.

118. The method of claim 50, wherein the channel is a microchannel.

119. The apparatus of claim 80, wherein the channel is a microchannel.

L23: Entry 11 of 94 File: USPT Jan 22, 2002

US-PAT-NO: 6340568
DOCUMENT-IDENTIFIER: US 6340568 B1

TITLE: Method for detecting and classifying nucleic acid hybridization

L23: Entry 11 of 94 File: USPT Jan 22, 2002

US-PAT-NO: 6340568
DOCUMENT-IDENTIFIER: US 6340568 B1

TITLE: Method for detecting and classifying nucleic acid hybridization

DATE-ISSUED: January 22, 2002

US-CL-CURRENT: 435/6

APPL-NO: 9/ 839860
DATE FILED: April 19, 2001

PARENT-CASE:

CROSS-REFERENCES TO RELATED APPLICATIONS
This application is a continuation of U.S. application Ser. No. 09/365,581, filed Aug. 2, 1999, which is a continuation-in-part of U.S. application Ser. No. 09/243,194, filed Feb. 1, 1999, which claims the benefit of U.S. Provisional Application No. 60/073,445, filed Feb. 2, 1998. This application also claims the benefit of U.S. Provisional Application No. 60/134,740, filed May 18, 1999. This application is also related to U.S. Application Ser. No. 09/365,978, filed Aug. 2, 1999. Each of these applications is incorporated herein by reference in its entirety for all purposes.

L23: Entry 11 of 94 File: USPT Jan 22, 2002

DOCUMENT-IDENTIFIER: US 6340568 B1
TITLE: Method for detecting and classifying nucleic acid hybridization

Detailed Description Paragraph Right (14):
The term "bio-assay system" means the bio-assay device as described above, in connection with the components necessary to electromagnetically probe and detect the bio-assay device. These components include, but are not limited to, the signal path(s), substrate(s), electronic devices such as signal generators, oscilloscopes, and vector analyzers necessary to probe to and detect signals from the bio-assay device, microchips and microprocessors which can probe and detect electromagnetic signals and analyze data, and the like.

Detailed Description Paragraph Right (55):
The binding interactions of the system generally occurs within the bio-assay device, and in particular along the conductive layer (interface transmission line in FIGS. 1A-1C). The conductive layer is fabricated from materials having a morphology which is conducive to support the propagation of the high frequency test signal. The conductive surface is constructed from materials exhibiting appropriate conductivity over the desired test frequency range as well as possessing good molecular binding qualities as described above. Such materials include, but are not limited to gold, indium tin oxide (ITO), copper, silver, zinc, tin, antimony, gallium, cadmium, chromium, manganese, cobalt, iridium, platinum, mercury, titanium, aluminum, lead, iron, tungsten, nickel, tantalum, rhenium, osmium, thallium or alloys thereof. The conductive layer may also be formed from semiconducting materials which may be either crystalline or amorphous in structure, including chemically doped or pure carbon, silicon, germanium, gallium-arsenide, idium-gallium arsenide, or the like. The conductive material may also be formed from polymers especially those that are conductive such as polyacetylene, polythiophene and the like. The conductive layer may be thick or only several molecular layers in depth as the application requires. The conductive layer may be comprised of an evaporated thin metal layer or an epitaxial layer of gallium arsenide or other semiconductor materials rendered conductive through known semiconductor processing techniques. In addition, the conductive layer may be derivatized, the process by which

is well known, e.g., see Kumar et al., "Patterned Self-Assembled Monolayer and Mesoscale Phenomena," Accounts of Chemical Research, 28:219-226 (1995).

Detailed Description Paragraph Right (97):
The system of detection formed through use of the bioassay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fabrication technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, New York, 1990.

Detailed Description Paragraph Right (196):
The second general approach involves the synthesis of nucleic acid probes. One method involves synthesis of the probes according to standard automated techniques and then post-synthetic attachment of the probes to a support. See for example, Beaucage, Tetrahedron Lett., 22:1859-1862 (1981) and Needham-VanDevanter, et al., Nucleic Acids Res., 12:6159-6168 (1984), each of which is incorporated herein by reference in its entirety. A second broad category is the so-called "spatially directed oligonucleotide synthesis approach. Methods falling within this category further include, by way of illustration and not limitation, light-directed oligonucleotide synthesis, microlithography, application by ink jet, microchannel deposition to specific locations and sequestration by physical barriers.

Detailed Description Paragraph Right (198):
Other combinatorial methods which can be used to prepare arrays for use in the current invention include spotting reagents on the support using ink jet printers. See Pease et al., EP 728, 520, and Blanchard, et al. Biosensors and Bioelectronics II: 687-690 (1996), which are incorporated herein by reference in their entirety. Arrays can also be synthesized utilizing combinatorial chemistry by utilizing mechanically constrained flowpaths or microchannels to deliver monomers to cells of a support. See Winkler et al., EP 624,059; WO 93/09668; and U.S. Pat. No. 5,885,837, each of which is incorporated herein by reference in its entirety.

Current US Original Classification (1):
435/6

Other Reference Publication (9):
Yershov et al., "DNA Analysis and Diagnostics on Oligonucleotide Microchips", Proc. Natl. Acad. Sci. USA, (1996) 93:4913-4918.

Other Reference Publication (29):
Gilles et al., "Single Nucleotide Polymorphic Discrimination by an Electronic Dot Blot Assay on Semiconductor Microchips", Nature Biotechnology, (1999) 17:365-370.

12. Document ID: US 6334980 B1

L23: Entry 12 of 94 File: USPT Jan 1, 2002

US-PAT-NO: 6334980
DOCUMENT-IDENTIFIER: US 6334980 B1

TITLE: Flexible apparatus with ablation formed chamber(s) for conducting bio-chemical analyses

L23: Entry 12 of 94 File: USPT Jan 1, 2002

US-PAT-NO: 6334980
DOCUMENT-IDENTIFIER: US 6334980 B1

TITLE: Flexible apparatus with ablation formed chamber(s) for conducting bio-chemical analyses

DATE-ISSUED: January 1, 2002

US-CL-CURRENT: 422/68.1; 422/129, 422/131, 422/134, 422/138, 422/50, 435/283.1, 435/285.1, 435/285.2, 435/286.1, 435/286.5, 435/287.1, 435/287.2, 435/287.3, 435/287.9, 435/289.1, 435/297.1, 435/303.1, 435/4, 435/6, 435/91.2

APPL-NO: 9/ 163063
DATE FILED: September 25, 1998

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATION
This application is a division of parent patent application No. 08/524,477, now U.S. Pat. No. 5,849,208 filed Sep. 7, 1995 by the same inventors for which benefit is claimed under 35 U.S.C. .sctn.120.

L23: Entry 12 of 94 File: USPT Jan 1, 2002

DOCUMENT-IDENTIFIER: US 6334980 B1
TITLE: Flexible apparatus with ablation formed chamber(s) for conducting bio-chemical analyses

Detailed Description Paragraph Right (30):
The groove center 180c is positioned a distance 162 from side 124b and a distance 164 from side 124a. Thus, when the layers of the substrate are assembled a thermocouple wire 182 installed in the groove 180 will be positioned in thermal contact with the center 160 of the reaction chamber floor 143 positioned in upper polyimide layer 122. The thermocouple wire 182 has ends 182a and 182b which terminate at or about side 124b and may connected to external circuitry by conventional means.

Detailed Description Paragraph Right (37):
The strips have interconnect pads 252a and 254a positioned at side 224b for connecting to an external power source. The interconnect pads can be positioned at any side or surface and may include conventional means for connecting to external circuitry. The strips also have fluid interface pads 252b and 254b. Both fluid pads are positioned a distance 272 from side 224b. Pad 252b is positioned a distance 274 from side 224a and pad 254b is positioned a distance 276 from pad 252a. Thus, when the layers of the substrate are assembled together, the fluid interface pad 252b is positioned directly beneath hole 270a and fluid interface pad 254b is positioned beneath hole 270b. A current path is provided between the fluid interface pads when the reaction chamber 240 is filled with fluid and the fluid is heated by the electrical resistance of the fluid as current is transmitted therethrough. The terminal strips are preferably formed of copper. Fluid pads 252b and 254b are preferably plated with a corrosion-resistant material such as platinum.

Current US Original Classification (1):
422/68.1

Current US Cross Reference Classification (1):
422/129

Current US Cross Reference Classification (2):
422/131

Current US Cross Reference Classification (3):

422/134

Current US Cross Reference Classification (4):
422/138

Current US Cross Reference Classification (5):
422/50

Current US Cross Reference Classification (6):
435/283.1

Current US Cross Reference Classification (7):
435/285.1

Current US Cross Reference Classification (8):
435/285.2

Current US Cross Reference Classification (9):
435/286.1

Current US Cross Reference Classification (10):
435/286.5

Current US Cross Reference Classification (11):
435/287.1

Current US Cross Reference Classification (12):
435/287.2

Current US Cross Reference Classification (13):
435/287.3

Current US Cross Reference Classification (14):
435/287.9

Current US Cross Reference Classification (15):
435/289.1

Current US Cross Reference Classification (16):
435/297.1

Current US Cross Reference Classification (17):
435/303.1

Current US Cross Reference Classification (18):
435/4

Current US Cross Reference Classification (19):
435/6

Current US Cross Reference Classification (20):
435/91.2

Other Reference Publication (2):
Eggers, Hogan, Reich, Lamture, Ehrlich, Hollis, Kosicki, Powdrill, Beattie, Smith, Varma, Gangadharam, Mallik, Burke and Wallace, ""A Microchip for Quantitative Detection of Molecules Utilizing Luminescent and Radioisotope Reporter Groups"," BioTechniques, vol. 17 (No. 3), pp. 516-523, (Jan. 15, 1994).

Other Reference Publication (5):
Bloomstein and Ehrlich, ""Laser-Chemical Three-dimensional Writing for Microelectromechanics and Application to Standard-cell Microfluidics"," J. Vac. Sci. Technol. B, p. 2671, (Nov. 15, 1992).

13. Document ID: US 6322683 B1

L23: Entry 13 of 94 File: USPT Nov 27, 2001

US-PAT-NO: 6322683
DOCUMENT-IDENTIFIER: US 6322683 B1

TITLE: Alignment of multicomponent microfabricated structures

L23: Entry 13 of 94 File: USPT Nov 27, 2001

US-PAT-NO: 6322683
DOCUMENT-IDENTIFIER: US 6322683 B1

TITLE: Alignment of multicomponent microfabricated structures

DATE-ISSUED: November 27, 2001

US-CL-CURRENT: 204/600; 204/601, 204/604

APPL-NO: 9/ 291808
DATE FILED: April 14, 1999

L23: Entry 13 of 94 File: USPT Nov 27, 2001

DOCUMENT-IDENTIFIER: US 6322683 B1
TITLE: Alignment of multicomponent microfabricated structures

Abstract Paragraph Left (1):
Microfluidic devices are fabricated by fabricating structures that are used to align elements that are to be attached to the devices or tools that are to be used in further fabrication steps on those devices. Elements to be attached include additional substrate layers, external sampling elements, e.g. capillaries, and the like. Preferred alignment structures include wells over which reservoirs are positioned, notches for use with alignment keys to align substrate layers or for receiving additional structural elements, and targets or guide holes for receiving tooling in further fabrication steps.

Brief Summary Paragraph Right (1):
The field of microfluidics has been held up as the next great advance in biological science, akin to the advances made in the electronics industry with the development of the microprocessor. In particular, the small scale, high level of accuracy and reproducibility, and ready automatability have led to expectations that this field of research will revolutionize the way work is done in research laboratories.

Brief Summary Paragraph Right (2):
As with the electronics industry, incremental advances will be achieved as the operations performed by these microfluidics systems are expanded and optimized in accordance with their increasing acceptance in the scientific area. However, also as with the electronics industry, the most significant developments in this technology will likely not involve incremental advances in specific operations, but will instead revolve around advances in the technology used to fabricate these systems. In particular, some of the most significant advances in the electronics industry have come from improved methods of producing microchips, which allow substantially increased efficiency and greater functionality in a smaller area or space.

Brief Summary Paragraph Right (3):
Fabrication of microfluidic systems typically involves the fabrication of grooves in the surface of a first substrate layer, which grooves will correspond to the channel network in a finished microfluidic device. A second substrate layer is overlaid and bonded to the first to seal the grooves thereby forming the channels. Apertures disposed in one of the substrates communicate with the channels and function as access ports and or reagent reservoirs for the devices. With certain exceptions, this fabrication process has been largely unimproved for some time. Commonly owned U.S. Pat. No. 5,882,465, to McReynolds, for example describes improved methods of mating and

bonding the various substrate layers together in order to improve fabrication efficiency. Similarly, Published International Patent Application No. WO 98/00705 describes methods for fabricating microfluidic devices used in high throughput assay applications.

Brief Summary Paragraph Right (4):
The present invention provides additional improvements in the fabrication of microfluidic devices, which improvements improve the efficiency both of the fabrication processes and operations to be performed by microfluidic devices.

Brief Summary Paragraph Right (5):
In a first aspect, the present invention provides a microfluidic device comprising a first substrate layer with at least a first planar surface. The first planar surface has at least a first microscale groove fabricated therein. The groove terminates at at least one end in a well also fabricated into the first surface. A second substrate layer comprising at least a first aperture disposed therethrough is also part of the device. The aperture is of smaller dimensions than the well. The second substrate layer is mated with the first surface of the first substrate layer to cover the groove and positioned such that the aperture is in complete communication with the well.

Brief Summary Paragraph Right (6):
Another aspect of the present invention is a method of fabricating a microfluidic device. First and second substrate layers are provided. A microscale groove is fabricated into at least a first surface of at least one of the first and second layers. Concurrently, an alignment structure is fabricated into the at least one surface of the first or second layers at a desired position relative to the microscale groove. One or more of a third component of the microfluidic device and a tool is mated with the alignment structure to align the third component or the tool relative to the microscale groove.

Brief Summary Paragraph Right (7):
A further aspect of the present invention is a method of fabricating a multilayered microfluidic device. A first substrate layer includes a first notch. A second notch is included in a second substrate layer. The first and second notches are positioned to be complementary when the first and second substrate layers are mated together. An alignment key is inserted into one of the first and second notches. The alignment key is configured to fit into the first and second notches when the first and second substrate layers are mated together and aligned in a first relative position. The first substrate layer is mated and bonded to the second substrate layer in the first relative position.

Drawing Description Paragraph Right (1):
FIG. 1 schematically illustrates microfluidic device comprised of a plurality of substrate layers where the microscale channel network is defined between the substrate layers.

Drawing Description Paragraph Right (4):
FIG. 4 illustrates one example of a microfluidic device that includes an external sampling pipettor element.

Drawing Description Paragraph Right (5):
FIG. 5 illustrates a microfluidic device coupled with appropriate controller and detector instrumentation for accessing externally stored materials.

Drawing Description Paragraph Right (6):
FIG. 6 illustrates an alignment structure for use in facilitating the fabrication of additional elements on a substrate of a microfluidic device, e.g., for drilling holes through the substrate.

Drawing Description Paragraph Right (7):
FIGS. 7A-B illustrate the use of an alignment key in the fabrication of microfluidic devices. As illustrated, the alignment key is also an external pipettor element.

Detailed Description Paragraph Right (1):
The present invention is generally directed to microfluidic devices and systems, and improved methods of manufacturing these devices and systems. In particular, the methods of the present invention facilitate the manufacture of microfluidic devices by facilitating either the fabrication of elements on those devices or the joining of additional elements to those devices, and particularly to the microscale channel

networks contained therein.

Detailed Description Paragraph Right (2):
As used herein, the term "microscale" or "microfabricated" generally refers to structural elements or features of a device which have at least one fabricated dimension in the range of from about 0.1 .mu.m to about 500 .mu.m. Thus, a device referred to as being microfabricated or microscale will include at least one structural element or feature having such a dimension. When used to describe a fluidic element, such as a passage, chamber or conduit, the terms "microscale," "microfabricated" or "microfluidic" generally refer to one or more fluid passages, chambers or conduits which have at least one internal cross-sectional dimension, e.g., depth, width, length, diameter, etc., that is less than 500 .mu.m, and typically between about 0.1 .mu.m and about 500 .mu.m. In the devices of the present invention, the microscale channels or chambers preferably have at least one cross-sectional dimension between about 0.1 .mu.m and 200 .mu.m, more preferably between about 0.1 .mu.m and 100 .mu.m, and often between about 0.1 .mu.m and 20 .mu.m. Accordingly, the microfluidic devices or systems prepared in accordance with the present invention typically include at least one microscale channel, usually at least two intersecting microscale channels, and often, three or more intersecting channels disposed within a single body structure. Channel intersections may exist in a number of formats, including cross intersections, "T" intersections, or any number of other structures whereby two channels are in fluid communication.

Detailed Description Paragraph Right (3):
The body structure of the microfluidic devices described herein typically comprises an aggregation of two or more separate layers which when appropriately mated or joined together, form the microfluidic device of the invention, e.g., containing the channels and/or chambers described herein. Typically, the microfluidic devices described herein will comprise a top portion, a bottom portion, and an interior portion, wherein the interior portion substantially defines the channels and chambers of the device.

Detailed Description Paragraph Right (4):
FIG. 1 illustrates an example of a two-layer body structure 10, for a microfluidic device. As shown, the bottom portion of the device 12 comprises a solid substrate that is substantially planar in structure, and which has at least one substantially flat upper surface 14. A variety of substrate materials may be employed as the bottom portion. Typically, because the devices are microfabricated, substrate materials will be selected based upon their compatibility with known microfabrication techniques, e.g., photolithography, wet chemical etching, laser ablation, air abrasion techniques, injection molding, embossing, and other techniques. The substrate materials are also generally selected for their compatibility with the full range of conditions to which the microfluidic devices may be exposed, including extremes of pH, temperature, salt concentration, and application of electric fields. Accordingly, in some preferred aspects, the substrate material may include materials normally associated with the semiconductor industry in which such microfabrication techniques are regularly employed, including, e.g., silica based substrates, such as glass, quartz, silicon or polysilicon, as well as other substrate materials, such as gallium arsenide and the like. In the case of semiconductive materials, it will often be desirable to provide an insulating coating or layer, e.g., silicon oxide, over the substrate material, and particularly in those applications where electric fields are to be applied to the device or its contents.

Detailed Description Paragraph Right (5):
In additional preferred aspects, the substrate materials will comprise polymeric materials, e.g., plastics, such as polymethylmethacrylate (PMMA), polycarbonate, polytetrafluoroethylene (TEFLON.TM.), polyvinylchloride (PVC), polydimethylsiloxane (PDMS), polysulfone, polystyrene, polymethylpentene, polypropylene, polyethylene, polyvinylidine fluoride, ABS (acrylonitrile-butadiene-styrene copolymer), and the like. Such polymeric substrates are readily manufactured using available microfabrication techniques, as described above, or from microfabricated masters, using well known molding techniques, such as injection molding, embossing or stamping, by polymerizing the polymeric precursor material within the mold (See U.S. Pat. No. 5,512,131), or by laser ablation techniques. Such polymeric substrate materials are preferred for their ease of manufacture, low cost and disposability, as well as their general inertness to most extreme reaction conditions. Again, these polymeric materials may include treated surfaces, e.g., derivatized or coated surfaces, to enhance their utility in the microfluidic system, e.g., provide enhanced fluid direction, e.g., as described in U.S. Pat. No. 5,885,470 which is incorporated herein by reference in its entirety for all purposes.

Detailed Description Paragraph Right (6):
The channels and/or chambers of the microfluidic devices are typically fabricated into the upper surface of the bottom substrate or portion 12, as microscale grooves or indentations 16, using the above described microfabrication techniques. The top portion or substrate 18 also comprises a first planar surface 20, and a second surface 22 opposite the first planar surface 20. In the microfluidic devices prepared in accordance with the methods described herein, the top portion also includes a plurality of apertures, holes or ports 24 disposed therethrough, e.g., from the first planar surface 20 to the second surface 22 opposite the first planar surface. The upper substrate is then overlaid and bonded to the upper surface of the lower substrate, whereby the grooves are sealed to form channels. The apertures disposed through the upper substrate then become wells or reservoirs that are in fluid communication with the termini of the channels in the finished layered device.

Detailed Description Paragraph Right (8):
Alternatively, pressure-based fluid transport methods may be used. In such cases, a pressure differential is created across the length of the channel segment through which fluid flow is desired, forcing or drawing the fluid through that channel. Establishing these pressure differentials may be accomplished by, e.g., applying positive pressures to the reservoirs at one end of a channel system, or alternatively, applying a negative pressure to a waste reservoir. Methods of engineering channel systems to simplify the application of pressure and/or vacuum is described in, e.g., U.S. patent application Ser. No. 09/277,367, filed Mar. 26, 1999, and incorporated herein by reference in its entirety for all purposes. Alternative pressure-based systems employ integrated pumps and valves within the body structure of a microfluidic device to drive fluid movement through the channels of the device in a controlled fashion. Such integrated pumps and valves are described in, e.g., Published International Patent Application No. WO 97/02357. In still other alternative pressure-based systems, a wicking material may be employed to draw fluids or other materials through the channels of the device, by placing the absorbent wicking material at an outlet port of one or more of the channels of the device. The wicking material then draws fluid out of the channel thereby creating a pressure differential to pull fluid through the channel.

Detailed Description Paragraph Right (9):
Because of their extremely small size, as well as their use in extremely sensitive and accurate analyses, slight variations in fabrication among different microfluidic devices can have substantial effects on the operation of those devices. As a result, it is desirable to ensure the most accurate fabrication methods. In accordance with the present invention, these methods utilize improved methods of aligning either the tooling which is used to fabricate such devices, or additional elements that are to be attached or otherwise joined with those devices or portions thereof.

Detailed Description Paragraph Right (10):
For example, regardless of whether a microfluidic device utilizes pressure based material transport or electrokinetic methods, inconsistencies in manufacturing can lead to inconsistencies in the flow of material through the channels of the device. In the typical fabrication of a microfluidic channel network, e.g., as described above, the upper substrate layer, e.g., that incorporating the reservoirs or wells, is overlaid upon the lower substrate layer, e.g., the layer incorporating the network of grooves or channels. Positioning of the reservoirs over the channels or grooves can affect the length of the channels. Specifically, if the upper layer is shifted to one side, it may cover or uncover more of the channel. In order to fabricate efficient, useful systems, tolerances are set for the alignment process. Similarly, tolerances are set for the fabrication of the channels and apertures, e.g., tolerances for size and position.

Detailed Description Paragraph Right (14):
The present invention addresses the above-described inconsistencies in manufacture of channel networks. In particular, in at least a first aspect, the present invention provides microfluidic devices, which are fabricated from multiple layers. The first substrate layer typically includes at least a first planar surface having at least a first microscale groove fabricated therein. In addition, the surface also typically includes a well or depression also fabricated therein, such that the groove terminates at at least one of its ends in the well. The well is configured such that the aperture provided within the second covering substrate layer will more easily be positioned entirely over the well. Specifically, the well is typically provided with cross-sectional dimensions that are markedly larger than the cross sectional dimensions of the aperture (or the aperture is dimensioned smaller than the well), so as to provide a relatively larger target to hit when assembling the layers. Accordingly, the

aperture in the assembled device will be in complete communication with the well. By "in complete communication" is meant that the aperture opening at the interface of the two substrate layers is entirely included by the well.

Detailed Description Paragraph Right (18):
As noted above, typically the microfluidic devices include a number of channels which connect a plurality of reservoirs, e.g., e.g., one, two, three, five, ten or more different channels which may or may not intersect one or more of the other channels. As such, the channels (also termed a channel network) will typically each terminate in one of a plurality of separate wells, which, in turn, are in complete communication with a plurality of separate apertures in the assembled device.

Detailed Description Paragraph Right (23):
The present invention also addresses other inconsistencies of the fabrication process through a similar mechanism, namely the inclusion of alignment facilitating elements in the fabrication process, such that alignment of a first structural element with a second structural element is dictated by the fabrication of the first element. One example where this is particularly useful is in the fabrication of microfluidic devices that incorporate external fluidic elements that must be integrated with internal fluidic elements. One example of such devices is that which includes an external capillary element for accessing externally stored samples.

Detailed Description Paragraph Right (24):
FIG. 4 is a schematic illustration of a microfluidic device and integrated pipettor element from a top (Panel A), side (Panel B) and perspective view (Panel C). As shown, the device 400 includes a main body structure 402 that includes a channel network disposed in its interior. The channel network includes a main analysis channel 404, which fluidly connects a sample inlet 406 with waste reservoir 408. Two reagent reservoirs 410 and 412 are provided in fluid communication with the analysis channel 404 via channels 414 and 416, respectively. Reagent reservoirs 410 and 412 are paired with buffer/diluent reservoirs 418 and 420, respectively, which are in communication with channels 414 and 416 via channels 422 and 424, respectively. In order to prevent electrolytic degradation of reagent and/or buffer materials, each of reservoirs 408, 410, 412, 416 and 420 is provided in electrical and/or fluid communication with an electrical access reservoir/salt bridge channel 428a/b, 430a/b, 432a/b, 434a/b, and 436a/b, respectively. The provision of an electrical access reservoir/salt bridge allows the application of voltages via electrodes for long periods of time without resulting in substantial degradation of reagents, buffers or the like. It should be noted that as reservoir 408 is a waste well, it typically does not require a separate electrical access reservoir/salt bridge, e.g., 428a/b.

Detailed Description Paragraph Right (26):
FIG. 5 is a schematic illustration of a microfluidic device incorporating an integrated pipettor element, as well as the overall material transport control and detection system, which incorporates the microfluidic device. As shown, the system 500 includes a microfluidic device 400, which incorporates an integrated pipettor/capillary element 438. Each of the electrical access reservoirs 428a-436a, has a separate electrode 528-536 disposed therein, e.g., contacting the fluid in the reservoirs. Each of the electrodes 528-536 is operably coupled to an electrical controller 502 that is capable of delivering multiple different voltages and/or currents through the various electrodes. Additional electrode 538, also operably coupled to controller 502, is positioned so as to be placed in electrical contact with the material that is to be sampled, e.g., in multiwell plate 540, when the capillary element 438 is dipped into the material. For example, electrode 538 may be an electrically conductive coating applied over capillary 438 and connected to an electrical lead which is operably coupled to controller 502. Alternatively, electrode 538 may simply include an electrode wire positioned adjacent the capillary so that it will be immersed in/contacted with the sample material along with the end of the capillary element 538. Alternatively, the electrode may be associated with the source of material, as a conductive coating on the material source well or as a conductive material from which the source well was fabricated. Establishing an electric field then simply requires contacting the electrical lead with the source well material or coating. Additional materials are sampled from different wells on the multiwell plate 540, by moving one or more of the plate 540 and/or device 400 relative to each other prior to immersing the pipettor 438 into a well. Such movement is typically accomplished by placing one or more of the device 400 or multiwell plate 540 on a translation stage, e.g., the schematically illustrated x-y-z translation stage 542.

Detailed Description Paragraph Right (27):

In at least one aspect, the capillary element includes at least one end that is substantially rectangular, so as to easily mate with a corresponding substantially rectangular opening on the body structure of the microfluidic device during fabrication of the overall device. Rectangular capillaries for use as the capillary element are generally commercially available, e.g., from VitroCom, Inc. or Mindrum Precision Products, Inc.

Detailed Description Paragraph Right (28):
In fabricating these pipettor devices, component alignment can yield a number of problems in addition to those recited above. Most notably, fabrication of reservoirs or apertures, and/or attachment of an external capillary element must be precisely positioned in order that the channel in the external capillary element is aligned with the channel(s) in the interior of the device. For example, in some cases, an external sampling capillary element is attached to a microfluidic device by drilling a hole into the body structure of the device, or a layer of the device, into which the capillary is inserted. Typically, the hole for the capillary element is disposed in the substrate layer that does not have the channel fabricated into it. This allows the capillary element to be completely inserted into the hole without blocking the channel in the body structure. Of course, this also requires precise alignment of the hole in one substrate layer with the channel in the other layer, so that the channel in the capillary communicates with the channel in the body structure. As such, an alignment mark is typically fabricated onto the channel bearing substrate at the same time as the channels, in order to align the hole with the channel in the opposing substrate.

Detailed Description Paragraph Right (34):
Because the opening 742 in the body structure is substantially rectangular, it is more conveniently fabricated than circular openings. In particular, while circular openings are typically drilled or air abraded into a body structure, rectangular openings are more conveniently fabricated by fabricating rectangular notches in two substrates by, e.g., photolithographic methods, which substrates are mated to define the body structure of the device. The two notches are positioned to provide a single rectangular opening in the side of the body structure. FIG. 7B illustrates an expanded view of the joining of a rectangular capillary with a two-layer microfluidic device. As shown, the device comprises a two-layer body structure including the above-described notches. As shown, the body structure 702 is made up of at least first and second planar substrates 702a and 702b, respectively. The upper surface of the lower substrate 702a includes grooves fabricated therein, which correspond to the desired channel structure of the finished device, e.g., groove 704. The upper substrate 702b is mated and bonded to the upper surface of the lower substrate 702a (as illustrated by the dashed arrows). Typically, bonding is carried out by thermal bonding techniques, which result in a single integrated unit having sealed channels or conduits running through its interior. The upper substrate also typically includes a number of holes disposed through it (not shown), which holes align with and provide access to the channels of the finished device. The lower and upper substrates also include notches 742a and 742b, respectively, which are aligned when the two substrates are mated, to define an opening.

Current US Original Classification (1):
204/600

Current US Cross Reference Classification (1):
204/601

Current US Cross Reference Classification (2):
204/604

Other Reference Publication (2):
Cohen, C. B. et al., "A Microchip-Based Enzyme Assay for Protein Kinase A," Anal. Chem. (1999) 273:89-97.

Other Reference Publication (6):
Harmon, B. J. et al., "Mathematical Treatment of Electrophoretically Mediated Microanalysis," Anal. Chem. (1993) 65:2655-2662.

Other Reference Publication (7):
Harmon, B. J. et al., "Selectivity in Electrophoretically Mediated Microanalysis by Control of Product Detection Time," Anal. Chem. (1994) 66:3797-3805.

Other Reference Publication (11):

Jacobson, S. C. et al., "Effects of Injection Schemes and Column Geometry on the Performance of Microchip Electrophoresis Devices," Anal. Chem. (1994) 66:1107-1113.

Other Reference Publication (12):
Jacobson, S. C. et al., "High-Speed Separations on a Microchip," Anal. Chem. (1994) 66:1114-1118.

Other Reference Publication (13):
Jacobson, S. C. et al., "Open Channel Electrochromatography on a Microchip," Anal. Chem. (1994) 66:2369-2373.

Other Reference Publication (14):
Jacobson S. C. et al., "Precolumn Reactions with Electrophoretic Analysis Integrated on a Microchip," Anal. Chem. (1994) 66:4127-4132.

Other Reference Publication (15):
Jacobson, S. C. et al., "Microchip electrophoresis with sample stacking," Electrophoresis (1995) 16:481-486.

Other Reference Publication (16):
Jacobson, S. C. et al., "Fused Quartz Substrates for Microchip Electrophoresis," Anal. Chem. (1995) 67:2059-2063.

CLAIMS:

1. A microfluidic device, comprising:

a first substrate layer comprising at least a first planar surface having at least a first microscale groove fabricated therein, the groove terminating at at least one end in a well also fabricated into the first surface; and

a second substrate layer comprising at least a first aperture disposed therethrough, the aperture being of smaller dimensions than the well, wherein the second substrate layer is mated with the first surface of the first substrate layer to cover the groove and positioned such that the aperture is in complete communication with the well.

2. The microfluidic device of claim 1, wherein the well and aperture are circular.

3. The microfluidic device of claim 2, wherein the well comprises a diameter that is at least 2% larger than a diameter of the aperture.

4. The microfluidic device of claim 2, wherein the well comprises a diameter that is at least 5% larger than a diameter of the aperture.

5. The microfluidic device of claim 2, wherein the well comprises a diameter that is at least 10% larger than a diameter of the aperture.

6. The microfluidic device of claim 2, wherein the well comprises a diameter that is at least 20% larger than a diameter of the aperture.

7. The microfluidic device of claim 1, wherein the well comprises a diameter of between about 1 mm and about 10 mm.

8. The microfluidic device of claim 1, wherein the aperture comprises a diameter of between about 1 mm and about 10 mm.

9. The microfluidic device of claim 1, wherein the groove terminates at a second well at a second end, and wherein the second substrate comprises a second aperture, the second aperture being positioned to be in complete communication with the second well when the second substrate is mated with the first surface of the first substrate layer.

10. The microfluidic device of claim 9, further comprising at least a first and second electrode disposed within the first and second apertures of the microfluidic device.

11. The microfluidic device of claim 1, further comprising a pressure or vacuum source operably coupled to the first aperture of the microfluidic device.

12. The microfluidic device of claim 1, wherein the first substrate surface comprises a

silica-based substrate, and the first groove and well are etched into the first surface.

13. The microfluidic device of claim 1, wherein the first surface of the first substrate comprises a polymeric material.

14. The microfluidic device of claim 13, wherein the polymeric material is selected from polymethylmethacrylate (PMMA), polycarbonate, polytetrafluoroethylene, polyvinylchloride (PVC), polydimethylsiloxane (PDMS), polysulfone, polystyrene, polymethylpentene, polypropylene, polyethylene, polyvinylidine fluoride, and ABS (acrylonitrile-butadiene-styrene copolymer).

15. The microfluidic device of claim 13, wherein the first groove and well are fabricated into the first surface of the first substrate by injection molding.

16. The microfluidic device of claim 13, wherein the first groove and well are fabricated into the first surface of the first substrate by embossing the groove and well into the first surface.

17. The microfluidic device of claim 13, wherein the first groove and well are fabricated into the first surface of the first substrate by laser ablating the groove and well into the first surface.

18. The microfluidic device of claim 1, further comprising at least a second groove fabricated into the first surface of the first substrate, the second groove terminating in at least a second well, wherein the second substrate comprises a second aperture, the second aperture being positioned to be in complete communication with the second well when the second substrate is mated with the first surface of the first substrate layer.

19. The microfluidic device of claim 10, wherein the second groove intersects with the first groove.

14. Document ID: US 6319670 B1

L23: Entry 14 of 94 File: USPT Nov 20, 2001

US-PAT-NO: 6319670
DOCUMENT-IDENTIFIER: US 6319670 B1

TITLE: Methods and apparatus for improved luminescence assays using microparticles

L23: Entry 14 of 94 File: USPT Nov 20, 2001

US-PAT-NO: 6319670
DOCUMENT-IDENTIFIER: US 6319670 B1

TITLE: Methods and apparatus for improved luminescence assays using microparticles

DATE-ISSUED: November 20, 2001

US-CL-CURRENT: 435/6; 436/534

APPL-NO: 8/ 998137
DATE FILED: December 23, 1997

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATION
This application is a continuation-in-part of U.S. application Ser. No. 08/954,355 filed Oct. 20, 1997, incorporated herein by reference, which is a continuation of U.S.

application Ser. No. 08/437,348, filed May 9, 1995 (now U.S. No. 5,679,519), incorporated herein by reference.

L23: Entry 14 of 94 File: USPT Nov 20, 2001

DOCUMENT-IDENTIFIER: US 6319670 B1
TITLE: Methods and apparatus for improved luminescence assays using microparticles

Assignee Name (1):
Meso Scale Technology LLP

Assignee Name (Derived) (1):
Meso Scale Technology LLP

Detailed Description Paragraph Right (13):
Alternatively, the assay-ligand may be immobilized by adsorption and/or covalent attachment to a "binding layer" coated on the surface of the particle. For example, an assay-ligand may be covalently attached to an oxide surface (e.g., silica or tin oxide) by attachment to functional groups introduced on the surface of the particle (these functional groups may be introduced by methods well-known in the art, e.g., by coating the particle with a self-assembled layer of a functionalized monomer such as a silane. Similarly, an assay-ligand may be covalently attached to the gold surface of a gold particle by coating the particle by reaction with a functionalized thiol (e.g., to form a self-assembled monolayer), see, e.g., U.S. Pat. No. 5,384,073. Assay-ligands can be attached to microparticles by attachment to an adsorbed layer of material (e.g., a protein or a polymer), see, e.g., Mrsny et al., Eur. J. Cell. Biol., 1988, 45:200. Preferably, coatings for conductive particles may have one or more of the following properties so as to promote the microparticle to act as an electrode for generating ECL: i) the binding layer is itself at least partially conductive; ii) the binding layer is thin (preferably<5nm) and/or iii) the binding layer does not completely coat the surface of the microparticle (e.g., there are defects in the binding layer so as for allow conduction of electrons through or around the binding layer) during the ECL reaction.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
436/534

15. Document ID: US 6319468 B1

L23: Entry 15 of 94 File: USPT Nov 20, 2001

US-PAT-NO: 6319468
DOCUMENT-IDENTIFIER: US 6319468 B1

TITLE: Affinity binding-based system for detecting particulates in a fluid

L23: Entry 15 of 94 File: USPT Nov 20, 2001

US-PAT-NO: 6319468
DOCUMENT-IDENTIFIER: US 6319468 B1

TITLE: Affinity binding-based system for detecting particulates in a fluid

DATE-ISSUED: November 20, 2001

US-CL-CURRENT: 422/63; 210/109, 210/374, 210/380.1, 210/780, 210/781, 210/787, 422/101,

422/102, 422/50, 422/64, 422/67 , 422/68.1, 422/72, 435/7.1, 435/7.2, 435/7.21, 436/177, 436/180, 436/45, 436/63

APPL-NO: 9/ 614834
DATE FILED: July 12, 2000

PARENT-CASE:

THIS APPLICATION IS A DIV. OF Ser. No. 08/995,056 Dec. 19, 1997 now U.S. Pat. No. 6,143,247 WHICH IS A CIP OF Ser. No. 08/768,990 Dec. 18, 1996. THIS APPLICATION Ser. No. 09/614,834 Jul. 12, 2000 is a divisional application of U.S. Ser. No. 08/995,056, filed Dec. 19, 1997, now U.S. Pat. No. 6,143,247 which CLAIMS BENEFIT OF Ser. No. 60/034,327 Dec. 20, 1996 AND CLAIMS BENEFIT OF 60/000,819 Jun. 27, 1995.

L23: Entry 15 of 94 File: USPT Nov 20, 2001

DOCUMENT-IDENTIFIER: US 6319468 B1
TITLE: Affinity binding-based system for detecting particulates in a fluid

Brief Summary Paragraph Right (44):
In a second aspect of the invention, an affinity-binding based, analytical apparatus is provided that is a combination of two elements. The first element is a platform as described herein. In preferred embodiments of these aspects of the invention, the platform is a rotatable platform having a means for being rotated about a central axis comprising a rotational element, preferably a hole for a spindle. In these aspects of the invention various components of the platform are connected to one another by channels, most preferably microchannels as defined herein. The second element in this aspect of the invention is a device comprising a holding means for accommodating the platforms of the invention, most preferably also including detecting means for detecting particulates and most preferably cells on the platforms of the invention. In preferred embodiments, the devices of the invention are provided as a device that comprises rotating means and controlling means thereof, and components of a detecting means operably positioned to detect binding of particulates on the platform surface and most preferably in a detection or cell accumulation chamber of the platform. In these aspects of the invention, fluid displacement through the components of the platforms of the invention is motivated by centripetal force produced by rotation of the platform about the central axis at a speed and for a time determined by controlling means comprising the device. In a preferred embodiment, the platform and device comprise a disk and player/reader device as disclosed in co-owned and co-pending U.S. Ser. No. 08/768,990, filed Dec. 18, 1996 and incorporated by reference.

Detailed Description Paragraph Right (15):
Sample is applied to the detection or cell accumulation chamber of the platforms of the invention either directly or more preferably by transfer of a metered amount of a portion of the sample from a fluid sample input means to the chamber, for example, by the selective opening of valves controlling access to the chamber from the fluid sample input means. Said valves include but are not limited to microvalves as described in more detail below including mechanical, electrical and thermal valve mechanisms, as well as capillary microvalves wherein fluid flow is controlled by the relationship between capillary forces and centripetal forces acting on the fluid. Reagent reservoirs, wash buffer reservoirs, other fluidic components and the contents thereof are connected to one another and to the detection and cell accumulation chamber through channels, preferably microchannels as defined herein, controlled by such valves. In preferred embodiments, delivery of fluids through such channels is achieved by the coincident rotation of the platform for a time and at a rotational velocity sufficient to motivate fluid movement between the desired components, and opening of the appropriate valves. The amount of a fluid, or a reagent comprising a fluid, delivered to the detection or cell accumulation chamber is thus controlled by the speed of rotation and the time during which the valve to the reagent reservoirs is open.

Detailed Description Paragraph Right (17):
In certain applications it may be desirable to increase the surface area available for specific binding by particles in order to increase the capacity for binding particles within a certain area of the device. The use of porous filter or tortuously-connected microchannels which have been treated with one half of the binding pair would provide such a high surface area.

Detailed Description Paragraph Right. (27):
In embodiments of the inventive platforms wherein the reflective metal layer is gold, the surface can be treated with omega-substituted alkanethiol compounds of general formula HS-(CH.sub.2).sub.n --R (where n is an integer from 1 to about 50, and R is an alkyl, alkenyl, alkynyl, aryl or alkaryl group, or substituted derivatives thereof), to form self-assembled monolayers (SAM). SAMs formed from poly(ethylene glycol) terminated alkane thiols (e.g., R=(CH.sub.2 CH.sub.2 O).sub.m CH.sub.3) resist protein adhesion (see Prime et al., 1993, J Amer. Chem. Soc. 115: 10714-10721) and have been used to block cell adhesion (see Singhvi et al., 1994, Science 264: 696-698). Gold surfaces have been coated with SAMs of hexadecanethiol (n=15, R=--CH.sub.3) to which laminin was adsorbed to provide a substrate suitable for cell attachment and growth (Singhvi et al., ibid.).

Detailed Description Paragraph Right (37):
The components of the platforms of the invention are in fluidic contract with one another. In preferred embodiments, fluidic contact is provided by microchannels comprising the surface of the platforms of the invention. Microchannel sizes are optimally determined by specific applications and by the amount of delivery rates required for each particular embodiment of the platforms and methods of the invention. Microchannel sizes can range from 0.1 .mu.m to a value close to the 1 mm thickness of the platform. Microchannel shapes can be trapezoid, circular or other geometric shapes as required. Microchannels preferably are embedded in a platform having a thickness of about 0.1 to 100 mm, wherein the cross-sectional dimension of the microchannels across the thickness dimension of the platform is less than 500 .mu.m and from 1 to 90 percent of said cross-sectional dimension of the platform.

Detailed Description Paragraph Right (39):
Examples of such microvalves include a piezo activator comprising a glass plate sandwiched between two silicon wafers, as described by Nakagawa et al. (1990, Proc. IEEE Workshop of Micro Electro Mechanical Systems, Napa Valley, Calif. pp. 89); a pneumatically-actuated microvalve, as described by Veider et al. (1995, Eurosensors IX, pp. 284-286, Stockholm, Sweden, Jun. 25-29); a micromachined gas valve (that is commercially available; Redwood Microsystems, Menlo Park, Calif.; ICSensors, Milpitas, Calif.); a pressure-balanced microvalve, as disclosed by Huff et al. (1994, 7.sup.th International Conference on Solid-State Sensors and Actuators, pp. 98-101); a polymeric relaxation valve; and a capillary microvalve. In the latter embodiment, which is based on the use of rotationally-induced fluid pressure to overcome capillary forces, it is recognized that fluid flow is dependent on the orientation of the surfaces of the components. Fluids which completely or partially wet the material of the microchannels, reservoirs, detection chambers, etc. (i.e., the components) of the platforms of the invention which contain them experience a resistance to flow when moving from a component of narrow cross-section to one of larger cross-section, while those fluids which do not wet these materials resist flowing from components of the platforms of the invention of large cross-section to those with smaller cross-section. This capillary pressure varies inversely with the sizes of the two components, or combinations thereof, the surface tension of the fluid, and the contact angle of the fluid on the material of the components. Generally, the details of the cross-sectional shape are not important, but the dependence on cross-sectional dimension results in microchannels of dimension less than 500 .mu.m exhibit significant capillary pressure. By varying the intersection shapes, materials and cross-sectional areas of the components of the platform of the invention, "valves" are fashioned that require the application of a particular pressure on the fluid to induce fluid flow. This pressure is applied in the disks of the invention by rotation of the disk (which has been shown above to vary with the square of the rotational frequency, with the radial position and with the extent of the fluid in the radial direction). By varying capillary valve cross-sectional dimensions as well as the position and extent along the radial direction of the fluid handling components of the platforms of the invention, capillary valves are formed to release fluid flow in a rotation-dependent manner, using rotation rates of from 100 rpm to several thousand rpm. This arrangement allows complex, multistep fluid processes to be carried out using a pre-determined, monotonic increase in rotational rate.

Detailed Description Paragraph Right (61):
In embodiments of the invention comprising rotatable disks, the device is a disk player/reader that controls the function of the disk. This device comprises mechanisms, spindles and motors that enable the disk to be loaded and spun, whereby fluid movement is centripetally-motivated as a consequence (i.e., the centripetal acceleration of the rotating disk causes the fluid to move through the microchannels and in the other fluidic components of the platform). In addition, the device provides means for a user to operate the disk and access and analyze data, preferably using a keypad and computer

display.

Detailed Description Paragraph Right (93):
Apparatus and methods for identifying particular cells or cell types in a biological sample are provided by the invention. A platform as described herein and in co-owned and co-pending U.S. Ser. No. 08/768,990, filed Dec. 18, 1996, incorporated by reference, is prepared by having a surface advantageously comprising a detection chamber adsorbably coated with monoclonal antibody specific to E. coli., the remaining sites on the surface comprising the detection chamber being blocked with bovine serum albumin (BSA). A milk sample is introduced onto the platform via a sample inlet port and brought into contact with the detection chamber comprising the surface coated with the antibody. The milk is incubated in this chamber for 30 min. The platform is then rotated to remove unwanted materials from the detection chamber and into a fluid waste receptacle with which the detection chamber is in fluid communication. An amount of a buffer appropriate for washing the chamber is then added to the surface of the chamber from a wash buffer reservoir with which the detection chamber is in fluid communication and containing a washing buffer, said buffer being motivated by centrifugal force and opening of a microvalve. In a useful embodiment, the washing buffer comprises an E. coli-specific monoclonal antibody covalently attached to an enzyme (such as peroxidase). This incubation is allowed to proceed for 5 min. The platform is again rotated with the opening of the appropriate microvalves to remove the washing solution from the chamber and to add a solution containing an enzymatic substrate (tetramethylbenzidine and hydrogen peroxide), maintained heretofore in a reagent reservoir with which the detection chamber is in fluid communication, preferably by a microvalve-controlled microchannel. The amount of E. coli bound in the reaction chamber is quantitated with regard to the amount of detected enzymatic activity, which is determined spectrophotometrically by the appearance of a light-absorbing product or the disappearance of a light-absorbing substrate.

Current US Original Classification (1):
422/63

Current US Cross Reference Classification (7):
422/101

Current US Cross Reference Classification (8):
422/102

Current US Cross Reference Classification (9):
422/50

Current US Cross Reference Classification (10):
422/64

Current US Cross Reference Classification (11):
422/67

Current US Cross Reference Classification (12):
422/68.1

Current US Cross Reference Classification (13):
422/72

Current US Cross Reference Classification (14):
435/7.1

Current US Cross Reference Classification (15):
435/7.2

Current US Cross Reference Classification (16):
435/7.21

Current US Cross Reference Classification (17):
436/177

Current US Cross Reference Classification (18):
436/180

Current US Cross Reference Classification (19):

436/45

Current US Cross Reference Classification (20):
436/63

CLAIMS:

1. A centripetally-motivated apparatus for detecting a particulate in a fluid, the apparatus comprising in combination

a platform, comprising a substrate having a first flat, planar surface and a second flat, planar surface opposite thereto, and an axis of rotation, wherein the first surface defines a detection chamber comprising an area that is coated with a specific binding reagent that specifically binds to the particulate to be detected, and further comprises a multiplicity of microchannels embedded within the first planar surface and a sample input means, wherein the detection chamber, the sample input means and the microchannels are connected and in fluid communication, and wherein the platform further comprises

a wash buffer reservoir containing a wash buffer in fluid communication with the detection chamber; and

a fluid waste receptacle in fluid communication with the detection chamber wherein the wash buffer reservoir and the sample input means are positioned on the first surface of the platform to be closer to the axis of rotation than is the detection chamber, and wherein the fluid waste receptacle is positioned on the surface of the platform to be farther from the axis of rotation than the detection chamber; the apparatus comprising the platform in combination with

a device, comprising a base, a rotating means, a power supply and user interface and operations controlling means, wherein the rotating means is operatively linked to the platform and in rotational contact therewith

wherein a fluid sample comprising a particulate is moved from the sample input means to the detection chamber by centripetal force arising from rotational motion of the platform for a time and a rotational velocity sufficient to move the fluid through the microchannels, and is incubated thereon for a time sufficient to result in specific binding between the particulate in the fluid sample and the specific binding reagent; and

wherein the fluid sample is replaced with the wash buffer and displaced into the fluid waste receptacle by centripetal force arising from rotational motion of the platform for a time and a rotational velocity sufficient to move the fluid through the microchannels; and

wherein the wash buffer is further displaced into the fluid waste receptacle by centripetal force arising from rotational motion of the platform for a time and a rotational velocity sufficient to move the fluid through the microchannels; and

wherein a particulate specifically bound to the detection chamber is detected thereupon.

16. Document ID: US 6312906 B1

L23: Entry 16 of 94 File: USPT Nov 6, 2001

US-PAT-NO: 6312906
DOCUMENT-IDENTIFIER: US 6312906 B1

TITLE: Immobilized nucleic acid hybridization reagent and method
L23: Entry 16 of 94 File: USPT Nov 6, 2001

US-PAT-NO: 6312906
DOCUMENT-IDENTIFIER: US 6312906 B1

TITLE: Immobilized nucleic acid hybridization reagent and method

DATE-ISSUED: November 6, 2001

US-CL-CURRENT: 435/6; 435/287.2, 536/24.3

APPL-NO: 9/ 482607
DATE FILED: January 14, 2000

PARENT-CASE:

This application claims priority to U.S. Ser. No. 60/116,063 filed on Jan. 15, 1999, and which is incorporated in its entirety by reference.
L23: Entry 16 of 94 File: USPT Nov 6, 2001

DOCUMENT-IDENTIFIER: US 6312906 B1
TITLE: Immobilized nucleic acid hybridization reagent and method

Detailed Description Paragraph Right (40):
According to this embodiment of the invention, individual species of probes are immobilized within densely packed pores or channels, arranged in patches across a wafer of solid support material. Known microfabrication techniques are available to produce microchannel or nanochannel glass and porous silicon useful as support wafers. Such flow-through devices, as conceived here can utilize a variety of conventional detection methods, including microfabricated optical and electronic detection components, film, charge-coupled-device arrays, camera systems and phosphor storage technology, to separately detect and or resolve a fluorescence signal for each species of probe.

Detailed Description Paragraph Right (41):
The invention is particularly useful in embodiments having multiple probe species immobilized in multiple microchannels and provides the following advantages over flat surface designs:

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/287.2

Other Reference Publication (8):
Yershov et al., "DNA Analysis And Diagnostics On Oligonucleotide Microchips", Proc. Natl. Acad. Sci. USA, vol. 93:4913-4918, (1996).

Other Reference Publication (14):
Lee et al., "Heterogeneous Catalysis On Platinum And Self-Assembled Monolayers On Metal And Metal Oxide Surfaces (Note a)", Pure & Appl. Chem., vol. 63(6):821-828, (1991).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

17. Document ID: US 6300141 B1
L23: Entry 17 of 94 File: USPT Oct 9, 2001

US-PAT-NO: 6300141
DOCUMENT-IDENTIFIER: US 6300141 B1

TITLE: Card-based biosensor device
L23: Entry 17 of 94 File: USPT Oct 9, 2001

US-PAT-NO: 6300141
DOCUMENT-IDENTIFIER: US 6300141 B1

TITLE: Card-based biosensor device

DATE-ISSUED: October 9, 2001

US-CL-CURRENT: 435/287.1; 204/228.1, 204/229.8, 204/230.2, 204/400, 204/403.01, 204/403.06, 204/406, 204/407, 204/409, 204/422, 349/1, 349/2, 349/33, 422/68.1, 422/82.01, 435/174, 435/176, 435/287.2, 435/288.7, 435/4, 435/6 , 435/7.1, 435/7.5, 435/7.92, 435/7.93, 436/164, 436/518, 436/524, 436/527, 436/536, 436/86

APPL-NO: 9/ 518178
DATE FILED: March 2, 2000

PARENT-CASE:

This application claims priority to U.S. Provisional Patent Application No. 60/122,546 filed Mar. 2, 1999, now pending, which is incorporated herein by reference.
L23: Entry 17 of 94 File: USPT Oct 9, 2001

DOCUMENT-IDENTIFIER: US 6300141 B1
TITLE: Card-based biosensor device

Brief Summary Paragraph Right (6):
The interest in biosensors is spurred by a number of potential advantages over strictly biochemical assay formats. First, electrochemical biosensors may be produced, using conventional microchip technology, in highly reproducible and miniaturized form, with the capability of placing a large number of biosensor elements on a single substrate (e.g., see U.S. Pat. Nos. 5,200,051 and 5,212,050).

Detailed Description Paragraph Right (32):
The sample-flow pathway 38 is preferably a channel or conduit between the sample-introduction region 12 and the biosensor 32. In one embodiment, the sample-flow pathway is an essentially unblocked passage or trench of a diameter suitable for conveying the liquid sample by capillary migration from the sample application region to the biosensor 32. Such a microfluidic trench can be formed by micromachining substrate material, e.g., as described in U.S. Pat. No. 5,194,133 or by injection molding. Liquid sample migrates in the sample flow pathway by capillary action or is driven by a micro-pump or by electroosmotic flow induced by suitably placed electrodes. As described hereinbelow, assay reagents are bound either in a releasable form or immobilized within the pathway 38. For example, the reagents can be bound to the walls of the pathway 38. In a preferred embodiment, along the length of the sample-flow pathway 38 is an insoluble bibulous material 74 for conveying the sample by capillarity and for binding assay reagents either in a releasable form or an immobilized form.

Detailed Description Paragraph Right (40):
Yet another embodiment of a biosensor module is shown in FIGS. 8C,8D. The device 600 includes a sample application port 610, microchannel 611, housing 614, biosensor chamber 612, filter element 616, porous support element 618, conjugate pad 620, and matrix element 622. Sample introduced at a sample application port 610 enters the top of the device and permeates the filter 616 which serves to remove particulate matter, such as cells. The conjugate pad 620 contains diffusively bound conjugate. Matrix 622 comprises a bibulous matrix containing non-diffusively bound analyte binding agent. Support element 618 supports the filter 616 and has openings therethrough for downward transfer, under the influence of gravity and also capillary action, of fluid from filter 616 into conjugate pad 620. The fluid mixes with HSP2/analyte conjugate in pad 620 and enters matrix 622. The fluid emerging from the matrix 622 enters biosensor 612. A plurality of separate biosensors can be arranged, preferably on a planar substrate,

to receive sample fluid delivered from microchannels emanating from a central sample application area (FIG. 8C). The module preferably includes a background control biosensor and a positive control biosensor in analogy with devices 11 (FIG. 8A) and 250 (FIG. 22) as described herein.

Detailed Description Paragraph Right (62):
Where HSP1 is embedded in a hydrocarbon-chain monolayer (FIGS. 14,15) the spacer anchoring the HSP1 peptide to the biosensor surface may be a hydrocarbon chain. The chain is preferably a fractional length of the chains making up the bilayer, such that the distal ends of the heterodimer which forms upon binding of the two peptides in the assembled monolayer are at or near the exposed surface of the monolayer. Thus, for example, if the monolayer is made up of 18-carbon chains, the spacer is preferably 2-10 carbons in length, depending on the length of the heterodimer.

Detailed Description Paragraph Right (83):
From the foregoing, it can be seen how various objects and advantages of the invention are met. The biosensor of the diagnostic card can be formed under controlled manufacturing conditions consistent with microchip scale and photomask processes, to produce highly uniform and/or miniaturized and/or high-density array biosensor devices with sample-introduction region, biosensor, and sample-flow pathway microfabricated on the substrate. The invention can incorporate multi-analyte assay surfaces by photomasking techniques that are capable of producing diagnostic devices having a plurality of unique sample-flow pathways, in fluid communication with highly reproducible biosensor elements.

Detailed Description Paragraph Right (126):
Where the heterodimer is embedded in a hydrocarbon-chain monolayer, as described below, the spacer anchoring the HSP1 peptide to the biosensor surface may be a hydrocarbon chain. The chain is preferably a fractional length of the chains making up the bilayer, such that the distal ends of the heterodimer peptides in the assembled monolayer are at or near the exposed surface of the monolayer. Thus, for example, if the monolayer is made up of 18-carbon chains, the spacer is preferably 2-10 carbons in length, depending on the length of the assembled heterodimer.

Current US Original Classification (1):
435/287.1

Current US Cross Reference Classification (1):
204/228.1

Current US Cross Reference Classification (2):
204/229.8

Current US Cross Reference Classification (3):
204/230.2

Current US Cross Reference Classification (4):
204/400

Current US Cross Reference Classification (5):
204/403.01

Current US Cross Reference Classification (6):
204/403.06

Current US Cross Reference Classification (7):
204/406

Current US Cross Reference Classification (8):
204/407

Current US Cross Reference Classification (9):
204/409

Current US Cross Reference Classification (10):
204/422

Current US Cross Reference Classification (14):
422/68.1

Current US Cross Reference Classification (15):
422/82.01

Current US Cross Reference Classification (16):
435/174

Current US Cross Reference Classification (17):
435/176

Current US Cross Reference Classification (18):
435/287.2

Current US Cross Reference Classification (19):
435/288.7

Current US Cross Reference Classification (20):
435/4

Current US Cross Reference Classification (21):
435/6

Current US Cross Reference Classification (22):
435/7.1

Current US Cross Reference Classification (23):
435/7.5

Current US Cross Reference Classification (24):
435/7.92

Current US Cross Reference Classification (25):
435/7.93

Current US Cross Reference Classification (26):
436/164

Current US Cross Reference Classification (27):
436/518

Current US Cross Reference Classification (28):
436/524

Current US Cross Reference Classification (29):
436/527

Current US Cross Reference Classification (30):
436/536

Current US Cross Reference Classification (31):
436/86

18. Document ID: US 6291188 B1

L23: Entry 18 of 94 File: USPT Sep 18, 2001

US-PAT-NO: 6291188
DOCUMENT-IDENTIFIER: US 6291188 B1

TITLE: Metallic solid supports modified with nucleic acids

L23: Entry 18 of 94 File: USPT Sep 18, 2001

US-PAT-NO: 6291188
DOCUMENT-IDENTIFIER: US 6291188 B1

TITLE: Metallic solid supports modified with nucleic acids

DATE-ISSUED: September 18, 2001

US-CL-CURRENT: 435/6; 427/58, 435/7.1

APPL-NO: 9/ 639311
DATE FILED: August 15, 2000

PARENT-CASE:

This is a continuation of application Ser. No. 08/808,750 filed Feb. 28, 1997 now abandoned and Ser. No. 08,475,051, filed Jun. 7, 1995, now U.S. Pat. No. 5,824,473.

L23: Entry 18 of 94 File: USPT Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6291188 B1
TITLE: Metallic solid supports modified with nucleic acids

Brief Summary Paragraph Right (58):
In a preferred embodiment, the blocking moieties, together with the modified nucleic acids, form a monolayer (sometimes referred to as a self-assembled monolayer (SAM)), as is generally understood by those in the art. The formation of a monolayer may be determined in several ways, as is appreciated by those in the art. The presence of a monolayer on at least a portion of the surface may be determined as is known in the art, for example by using ellipsometry, X-ray photoelectron spectroscopy, infrared external reflectance spectroscopy, or surface plasmon resonance.

Detailed Description Paragraph Right (2):
A self-assembled monolayer of modified nucleic acids and C.sub.16 blocking moieties with hydroxyl terminal groups was made.

Detailed Description Paragraph Right (11):
Hybridization of Labeled Oligonucleotides. All hybridization experiments were performed in 6.times.SSC (Saline Sodium Citrate, NaCl is 0.9 M, sodium citrate is 0.09M in 6.times.) at 37.degree. C. overnight. After hybridization, the sample was washed 3 times with 3.times.SSC buffer at room temperature for 10 minutes each and 1 time with 6.times.SSC at 40.degree. C. for 30 minutes. Samples that were hybridized with oligomer complementary with the one attached to the surface showed more than 10 times higher activity level than samples that were reacted with a non-complementary oligomer. Gold surfaces coated with HS--(CH.sub.2).sub.16 --OH monolayer, in the absence of nucleic acid, and reacted with either LS or LT did not show significant counts above the background activity. Therefore, the formation of a mixed self-assembled monolayer resulted in covalent attachment of DNA strands to the surface without significant losses in binding activity and specificity.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (2):
435/7.1

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (68):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified

Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (73):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (78):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (85):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (89):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of FE(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

Other Reference Publication (116):
Fotin, A. et al., "Parallel Thermodynamic Analysis of Duplexes on Oligodeoxyribonucleotide Microchips," Nucleic Acids Research, 216(6):1515-1521 (1998).

Other Reference Publication (117):
Guschin, D. et al., "Manual Manufacturing of Oligonucleotide, DNA, and Protein Microchips," Analytical Biochemistry, 250:203-211 (1997).

Other Reference Publication (118):
Dubiley, S. et al., "Factionation, phosphorylation and Ligation on Oligonucleotide Microchips to Enhance Sequencing by Hybridization," Nucleic Acids Research, 25(12):2259-2265 (1997).

Other Reference Publication (119):
Guschin, D. et al., "Oligonucleotide Microchips as Genosensors for Determinative and Environmental Studies in Microbiology," 63(6):2397-2402 (1997).

Other Reference Publication (125):
Parinov, S., "DNA Sequencing by Hybridization to Microchip octa- and Decanucleotide Extended by Stacked Pentanucleotides," Nucleic Acids Research, 24(15):2998-3004 (1996).

Other Reference Publication (126):
Yershov, G. et al., "DNA Analysis and Diagnostics on Oligonucleotide Microchips," Proc. Natl. Acad. Sci. USA, 93:4913-4918 (1996).

Other Reference Publication (129):
Proudnikov, D. "Immobilization of DNA in Polyacrylamide Gel for the manufacture of DNA and DNA-Oligonucleotide Microchips," Analytical Biochemistry, 259:34-41 (1998).

CLAIMS:

1. An array of nucleic acids comprising a solid support having a plurality of regions, each region comprising an electrode comprising a self-assembled monolayer comprising:

a) blocking moieties, having a first end attached to said electrode, wherein said blocking moieties shield nucleic acids from said electrode; and

b) at least one modified nucleic acid, comprising a nucleic acid and a linker moiety having a first and second end, wherein said first end of said linker is attached to said electrode and said second end is attached to said nucleic acid; wherein at least two different regions comprise different nucleic acids.

28. A method of hybridizing a probe nucleic acid to a target nucleic acid, said method comprising adding a target nucleic acid to an array of probe nucleic acids comprising a solid support having at plurality of regions, each region comprising an electrode comprising a self-assembled mixed monolayer comprising:

a) blocking moieties, having a first end attached to said electrode, wherein said blocking moieties shield nucleic acids from said electrode; and

b) at least one modified nucleic acid, comprising a probe nucleic acid and a linker moiety having a first and second end, wherein said first end of said linker is attached to said solid support and said second end is attached to said nucleic acid;

wherein at least two different regions comprise different probe nucleic acids; under conditions wherein at least one of said probe nucleic acids and said target nucleic acid will hybridize to form a hybridization complex.

19. Document ID: US 6287874 B1

L23: Entry 19 of 94 File: USPT Sep 11, 2001

US-PAT-NO: 6287874
DOCUMENT-IDENTIFIER: US 6287874 B1

TITLE: Methods for analyzing protein binding events

L23: Entry 19 of 94 File: USPT Sep 11, 2001

US-PAT-NO: 6287874
DOCUMENT-IDENTIFIER: US 6287874 B1

TITLE: Methods for analyzing protein binding events

DATE-ISSUED: September 11, 2001

US-CL-CURRENT: 436/501; 436/149, 436/86

APPL-NO: 9/ 365580
DATE FILED: August 2, 1999

PARENT-CASE:

CROSS-REFERENCES TO RELATED APPLICATIONS
This application is a continuation-in-part of U.S. application Ser. No. 09/243,194 filed Feb. 1, 1999, which claims the benefit of U.S. Provisional Application No. 60/073,445, filed Feb. 2, 1998. This application also claims the benefit of U.S. Provisional Application 60/134,740 filed May 18, 1999. This application is also related to U.S. application Ser. No. 09/365,978, filed Aug. 2, 1999 and U.S. application Ser. No. 09/365,581, filed Aug. 2, 1999, both of which were filed concurrently herewith. Each of these applications is incorporated herein by reference in their entirety for all purposes.

L23: Entry 19 of 94 File: USPT Sep 11, 2001

DOCUMENT-IDENTIFIER: US 6287874 B1
TITLE: Methods for analyzing protein binding events

Detailed Description Paragraph Right (29):
A "bio-assay system" refers to the bio-assay device as described above, in connection with the components necessary to electromagnetically probe and detect the bio-assay device. These components include, but are not limited to, the signal path(s), substrate(s), electronic devices such as signal generators, oscilloscopes, and vector analyzers necessary to probe to and detect signals from the bio-assay device,

microchips and microprocessors which can probe and detect electromagnetic signals and analyze data, and the like.

Detailed Description Paragraph Right (54):
The binding interactions of the system generally occurs within the bio-assay device, and in particular along the conductive layer (interface transmission line in FIGS. 1A-1C). The conductive layer is fabricated from materials having a morphology which is conducive to support the propagation of the high frequency test signal. The conductive surface is constructed from materials exhibiting appropriate conductivity over the desired test frequency range as well as possessing good molecular binding qualities as described above. Such materials include, but are not limited to gold, indium tin oxide (ITO), copper, silver, zinc, tin, antimony, gallium, cadmium, chromium, manganese, cobalt, iridium, platinum, mercury, titanium, aluminum, lead, iron, tungsten, nickel, tantalum, rhenium, osmium, thallium or alloys thereof. The conductive layer may also be formed from semiconducting materials which may be either crystalline or amorphous in structure, including chemically doped or pure carbon, silicon, germanium, gallium-arsenide, idium-gallium arsenide, or the like. The conductive material may also be formed from polymers especially those that are conductive such as polyacetylene, polythiophene and the like. The conductive layer may be thick or only several molecular layers in depth as the application requires. The conductive layer may be comprised of an evaporated thin metal layer or an epitaxial layer of gallium arsenide or other semiconductor materials rendered conductive through known semiconductor processing techniques. In addition, the conductive layer may be derivatized, the process by which is well known, e.g., see Kumar et al., "Patterned Self-Assembled Monolayer and Mesoscale Phenomena," Accounts of Chemical Research, 28:219-226 (1995).

Detailed Description Paragraph Right (98):
The system of detection formed through use of the bioassay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fabrication technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, N.Y., 1990.

Detailed Description Paragraph Right (244):
Regardless of the identity of the targets at the various array elements, a signal is launched down the signal path running to each element to monitor binding at each of the various elements. Modulations in the launched signal are used to detect binding between the target and a ligand in the sample. An array may be used in conjunction with a microfluidic device to controllably add microquantities of different samples to the different arrays. In the situation in which all the targets are identical, typically the fluidic device is used to dispense different samples to the various arrays; whereas, when the protein target in the various elements vary, the fluidic device dispenses the same sample to the different elements of the arrays.

Detailed Description Paragraph Right (248):
It is possible through the use or array and microfluidic technology to use the methods described herein in a high throughput screening process (HTS). In such an approach, hundreds of thousands of compounds are screened for their ability to bind a particular target or screened according to the higher levels of analysis described above. For example, the invention described herein can be miniaturized, so that highly parallel screening platforms can be realized; platforms which are capable of screening hundreds or thousands of compounds simultaneously, and at the same time determining the effect of binding (e.g. agonist or antagonist), affinity, kinetics, etc. Additionally, such miniature systems require very small amounts of compound, thus greatly saving costs in purchasing said compounds from combinatorial libraries.

Detailed Description Paragraph Right (249):

The system of detection formed through use of the bio-assay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. Using chip fabrication technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) can be manufactured. Using small volumes to minimize diffusion times and making kinetic measurements at only the start of the binding reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve.

Detailed Description Paragraph Left (35):
C. Coupling of Arrays and Microfluidic Devices

Current US Original Classification (1):
436/501

Current US Cross Reference Classification (1):
436/149

Current US Cross Reference Classification (2):
436/86

20. Document ID: US 6287776 B1

L23: Entry 20 of 94 File: USPT Sep 11, 2001

US-PAT-NO: 6287776
DOCUMENT-IDENTIFIER: US 6287776 B1

TITLE: Method for detecting and classifying nucleic acid hybridization

L23: Entry 20 of 94 File: USPT Sep 11, 2001

US-PAT-NO: 6287776
DOCUMENT-IDENTIFIER: US 6287776 B1

TITLE: Method for detecting and classifying nucleic acid hybridization

DATE-ISSUED: September 11, 2001

US-CL-CURRENT: 435/6; 435/283.1, 435/286.1, 435/287.2

APPL-NO: 9/ 365581
DATE FILED: August 2, 1999

PARENT-CASE:

CROSS-REFERENCES TO RELATED APPLICATIONS
This application is a continuation-in-part of U.S. application Ser. No. 09/243,194, filed Feb. 1, 1999, which claims the benefit of U.S. Provisional Application No. 60/073,445, filed Feb. 2, 1998. This application also claims the benefit of U.S. Provisional Application 60/134,740, filed May 18, 1999. This application is also related to a U.S. application entitled "Test Systems and Sensors for Detecting Molecular Binding Events," U.S. application Ser. No. 09/365,978, filed concurrently herewith on Aug. 2, 1999. Each of these applications is incorporated herein by

reference in its entirety for all purposes.

L23: Entry 20 of 94 File: USPT Sep 11, 2001

DOCUMENT-IDENTIFIER: US 6287776 B1
TITLE: Method for detecting and classifying nucleic acid hybridization

Detailed Description Paragraph Right (14):
The term "bio-assay system" means the bio-assay device as described above, in connection with the components necessary to electromagnetically probe and detect the bio-assay device. These components include, but are not limited to, the signal path(s), substrate(s), electronic devices such as signal generators, oscilloscopes, and vector analyzers necessary to probe to and detect signals from the bio-assay device, microchips and microprocessors which can probe and detect electromagnetic signals and analyze data, and the like.

Detailed Description Paragraph Right (55):
The binding interactions of the system generally occurs within the bio-assay device, and in particular along the conductive layer (interface transmission line in FIGS. 1A-1C). The conductive layer is fabricated from materials having a morphology which is conducive to support the propagation of the high frequency test signal. The conductive surface is constructed from materials exhibiting appropriate conductivity over the desired test frequency range as well as possessing good molecular binding qualities as described above. Such materials include, but are not limited to gold, indium tin oxide (ITO), copper, silver, zinc, tin, antimony, gallium, cadmium, chromium, manganese, cobalt, iridium, platinum, mercury, titanium, aluminum, lead, iron, tungsten, nickel, tantalum, rhenium, osmium, thallium or alloys thereof. The conductive layer may also be formed from semiconducting materials which may be either crystalline or amorphous in structure, including chemically doped or pure carbon, silicon, germanium, gallium-arsenide, idium-gallium arsenide, or the like. The conductive material may also be formed from polymers especially those that are conductive such as polyacetylene, polythiophene and the like. The conductive layer may be thick or only several molecular layers in depth as the application requires. The conductive layer may be comprised of an evaporated thin metal layer or an epitaxial layer of gallium arsenide or other semiconductor materials rendered conductive through known semiconductor processing techniques. In addition, the conductive layer may be derivatized, the process by which is well known, e.g., see Kumar et al., "Patterned Self-Assembled Monolayer and Mesoscale Phenomena," Accounts of Chemical Research, 28:219-226 (1995).

Detailed Description Paragraph Right (97):
The system of detection formed through use of the bioassay device provides a high throughput detection system because detection optionally occurs in real time and many samples can be rapidly analyzed. The response period is optionally monitored on a nanosecond time scale. As soon as the molecules are bound to each other, detection occurs. More time is optionally required to measure low concentrations or binding events between molecules with a low binding affinity. The actual time is optionally limited by diffusion rates. Other than these potential limitations, thousands of compounds are optionally run through the system very quickly, for example, in an hour. For example, using chip fabrication technologies, a 10,000 channel device (using some of the emerging microfluidics technologies) is possible, and with small volumes and thus short diffusion times, and kinetic measurements measuring only the beginning of the reaction, 10 million samples per hour are optionally measured. With known concentrations, the binding affinity is optionally calculated from the kinetics alone and thus the device can be probed at a very fast time scale and the affinity calculated and/or estimated from the slope of the kinetic curve. References for kinetics and affinities can be found in any standard biochemistry or chemistry text such as Mathews and van Holde, Biochemistry, Benjamin Cummings, New York, 1990.

Detailed Description Paragraph Right (196):
The second general approach involves the synthesis of nucleic acid probes. One method involves synthesis of the probes according to standard automated techniques and then post-synthetic attachment of the probes to a support. See for example, Beaucage, Tetrahedron Lett., 22:1859-1862 (1981) and Needham-VanDevanter, et al., Nucleic Acids Res., 12:6159-6168 (1984), each of which is incorporated herein by reference in its entirety. A second broad category is the so-called "spatially directed oligonucleotide synthesis approach. Methods falling within this category further include, by way of illustration and not limitation, light-directed oligonucleotide synthesis,

microlithography, application by ink jet, microchannel deposition to specific locations and sequestration by physical barriers.

Detailed Description Paragraph Right (198):
Other combinatorial methods which can be used to prepare arrays for use in the current invention include spotting reagents on the support using ink jet printers. See Pease et al., EP 728, 520, and Blanchard, et al. Biosensors and Bioelectronics II: 687-690 (1996), which are incorporated herein by reference in their entirety. Arrays can also be synthesized utilizing combinatorial chemistry by utilizing mechanically constrained flowpaths or microchannels to deliver monomers to cells of a support. See Winkler et al., EP 624,059; WO 93/09668; and U.S. Pat. No. 5,885,837, each of which is incorporated herein by reference in its entirety.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/283.1

Current US Cross Reference Classification (2):
435/286.1

Current US Cross Reference Classification (3):
435/287.2

Other Reference Publication (10):
Yershov, Gennady; Barsky, Victor; Belgovskiy, Alexander; Kirillov, Eugene; Kreindlin, Edward; Ivanov, Igor; Parinov, Sergei; Guschin, Dmitri; Alexsei, Drobishev, Aleksei and Dubiley, Svetlana; DNA analysis and diagnositcs on oligonucleotide microchips, Proc. Natl. Acad. Sci. USA, May, 1996, vol. 93, pp. 4913-4918.

Other Reference Publication (30):
Gilles, Patrick N.; Wu, David J.; Foster, Charles B.; Dillon, Patrick J. and Chanock, Stephen J.; Single nucleotide polymorphic discrimination by an electronic dot blot assay on simiconductor microchips, Nature Biotechnology, Apr., 1999, vol. 17, pp. 365-370.

21. Document ID: US 6287765 B1

L23: Entry 21 of 94 File: USPT Sep 11, 2001

US-PAT-NO: 6287765
DOCUMENT-IDENTIFIER: US 6287765 B1

TITLE: Methods for detecting and identifying single molecules

L23: Entry 21 of 94 File: USPT Sep 11, 2001

US-PAT-NO: 6287765
DOCUMENT-IDENTIFIER: US 6287765 B1

TITLE: Methods for detecting and identifying single molecules

DATE-ISSUED: September 11, 2001

US-CL-CURRENT: 435/6; 435/91.2, 536/22.1, 536/23.1, 536/24.3, 536/24.5

APPL-NO: 9/ 081930
DATE FILED: May 20, 1998

L23: Entry 21 of 94 File: USPT Sep 11, 2001

DOCUMENT-IDENTIFIER: US 6287765 B1
TITLE: Methods for detecting and identifying single molecules

Brief Summary Paragraph Right (343):
Whereas molecular adhesives of the instant invention are used to specifically attach two surfaces, molecular adherents are used to attach a first selected molecule to a second selected molecule comprising a surface. For example, a single nanofabricated surface may be functionalized by template-directed and feature-specific attachment of MOLECULAR MACHINES disclosed herein. For example, A selected molecule (e.g., a signal-generating molecule) or a multimolecular device (e.g., a fluorescence energy transfer complex) may be site-specifically delivered, e.g., to a selected, specifically attractive surface feature (e.g., an edge, pit, vertex, directrix or nadir). Advantageously, nonselected surfaces or parts need not be modified, even if they have the same chemical composition as selected surface features. Nonselected surfaces are not specifically attractive and therefore not specifically recognized. Because shape recognition is specific for a surface feature and not its chemical identity, monolithic nanoscale features on micromachined surfaces can be specifically decorated with useful MOLECULAR MACHINES. Feature-specific delivery of MOLECULAR MACHINES to nanofabricated shapes (e.g., diamondoid features of a carbon, silicon or gallium arsenide device) enables precise structural and functional integration of organic and inorganic surfaces and device components. Alternatively, optoelectronic MOLECULAR MACHINES patterned in a feature-directed manner to pits comprising CD and DVD surfaces can be used as marking devices for antipiracy and anticounterfeiting purposes.

Brief Summary Paragraph Right (461):
Structural shapes, structural features and surface features refer to specifically attractive surfaces, i.e., specifically recognizable structural features of a surface. Surface features include natural, synthetic, designed or selected structures or surfaces, preferably subnanometer- to submicron-sized surface contours, having a two-dimensional or three-dimensional shape, contour, texture, characteristic, pattern, distribution, property, configuration, arrangement, organization, order, lack of organization or order, form, trait or peculiarity that can be specifically recognized by a shape-specific recognition element. Structural shapes or surface features are optionally designed or selected to be specifically recognizable by a shape recognition partner, preferably a shape recognition partner selected from a diverse mixture of molecules comprising a library, advantageously a library of libraries. In a preferred mode of operation, surfaces are micromachined and/or nanofabricated with a variety of structural features, preferably a diversity of structural features, and coselected against shape recognition libraries. The shape recognition libraries are preferably nested combinatorial libraries of libraries exploring, e.g., nucleotide sequence, nucleotide charge, backbone modifications, sequence length, chemical modifications and optionally positional space (i.e., the relationship between pairs and groups of nucleotide modifications). Surface features that are specifically attractive, i.e., specifically recognizable by at least one member of a shape recognition library, are selected as useful prospects for template-directed assembly of MOLECULAR MACHINES. Alternatively, selected attractive features are used for surface-to-surface registration and bonding. In a particularly preferred aspect, diverse modifications are introduced in a single surface, preferably by randomized or combinatorial surface treatments, advantageously with nanoscale or atomic precision. Tagged molecules comprising diverse shape recognition libraries, preferably nucleic acid libraries or nucleotide-encoded chemical libraries, are then coselected against diverse surface features to identify useful specific pairs of specifically attractive surface shapes and shape-specific probes. Fluorescently tagged nucleic acids or nucleotide-encoded chemical libraries are preferred. surfaces are advantageously imaged by a combination of optical and scanning probe microscopy (SPM), preferably fluorescence and atomic force microscopy (AFM), before and after exposure to shape recognition libraries. Bound, fluorescently tagged molecules, preferably nucleotides, are then isolated and characterized, preferably by AFM extraction followed by single-molecule nucleic acid amplification and/or sequencing.

Brief Summary Paragraph Right (503):
In a preferred embodiment, multimolecular adhesives are designed for use in industrial environments, e.g., for alignment and specific attachment of nanoscale features comprising micromachined surfaces, e.g., physical and chemical sensors, semiconductors, microelectromechanical systems (MEMS) and MEMS devices, nanoelectromechanical systems (NEMS) and NEMS devices and ultraf ast molecular computers. Because industrial-use MEMS and NEMS devices and associated sensor, actuator and transducer surfaces represent

extremely harsh and unforgiving environments, nucleotide ligands, nucleotide receptors, aptamers and hybridizable nucleotides are preferred, even required, over more readily available ligands and receptors (e.g., antigens, antibodies, avidin, streptavidin, lectins, drug and hormone receptors). and receptors and are preferred over specific recognition. Protein-based antibodies and receptors currently used in diagnostic and analytical specific binding assays are not sufficiently robust to function for protracted intervals under the extreme and volatile thermal, chemical and electromechanical conditions operative during MEMS manufacture and use.

Brief Summary Paragraph Right (528):
In a particular preferred embodiment of the instant invention, one or more multimolecular structures or multimolecular devices is immobilized to a solid support comprising a transducer, i.e., a device and/or process capable of converting the output (e.g., matter, energy and/or heat) of a molecule or group of molecules comprising a multimolecular complex or multimolecular device to a different form of matter, energy and/or heat, preferably useful work or a detectable signal. Functional coupling between a multimolecular device of the invention (e.g., a multimolecular transducer, a multimolecular switch or a multimolecular sensor) and a transducer surface can occur, e.g., by the transfer of mass, energy, electrons or photons or by coupled chemical or enzymatic reactions that share a common intermediate, mediator or shuttle species. Transducers capable of converting matter, energy, data or information from a first form or state to a second form or state, include, without limitation, electronic, electrical, optical, optoelectronic, electromagnetic, mechanical, electromechanical, electrochemical, photochemical, thermal and acoustical devices. Transducers include, without limitation, batteries, marking devices, memory devices, mechanical devices, parts, motors and machines, optical fibers and waveguides, evanescent waveguides, light-addressable potentiometric devices, photovoltaic devices, photoelectric and photochemical and photoelectrochemical cells, conducting and semiconducting substrates, molecular and nanoscale wires, gates and switches, charge-coupled devices, photodiodes, electrical and optoelectronic switches, imaging and storage and photosensitive media (e.g., films, polymers, tapes, slides, crystals and liquid crystals), photorefractive devices, displays, optical disks, digital versatile disks, amperometric and potentiometric electrodes, ion-selective electrodes, field effect transistors, interdigitated electrodes and other capacitance-based devices, piezoelectric and microgravimetric devices, surface acoustic wave and surface plasmon resonance devices, thermistors, transmitters, receivers, signaling devices and the like. These and other transducers, transduction principles and related devices are known to those of skill in the art (e.g., Taylor (1990) Biosensors: Technology, Applications, and Markets, Decision Resources, Inc., Burlington Mass.).

Detailed Description Paragraph Right (62):
In an alternative mode of preparation, the first defined sequence segment of the PSA-binding synthetic heteropolymer described above is incorporated during the final stage of dendrimer polymerization rather than by hybridization of the synthetic heteropolymer to the completed dendrimer. The selected PSA-binding defined sequence segment is added to the dendrimer synthetic process during the final polymerization step either as a single-stranded defined sequence segment (i.e., "end") of an arm or as a double-stranded region (i.e., hybridized "middle") of two arms making up the partially double-stranded "monomer" used to assemble the outermost layer of the DNA dendrimer. Incorporation of this PSA-binding monomer yields a multivalent heteropolymeric hybrid structure having the specific binding capabilities of a first synthetic heteropolymer polymerized into a hyperbranched discrete heteropolymeric structure by means of a dendrimeric linker oligonucleotide. In a further modification of this approach, the PSA-binding synthetic heteropolymer is covalently attached to the 5' end of the outermost arm of the DNA dendrimer, rather than being attached by hybridization. Covalent attachment is accomplished either by enzymatic ligation or by heterobifunctional crosslinking to a 5'-terminal amine linker.

Detailed Description Paragraph Right (75):
One potentially attractive commercial application of tethered specific recognition principles exemplified in the preceding paragraphs is a molecular counting device, i.e. an array of multimolecular sensors capable of detecting and quantifying very few molecules in very small sample volumes, preferably even an individual molecule in a nanoliter or subnanoliter volume. Conventional affinity-based assays and sensors measure the concentration of an analyte by specific binding of some fraction of analyte molecules within a sample (i.e., a percentage of analyte molecules determined by reagent and analyte concentrations, equilibrium binding constants and the reagent and analyte masses per test). Quantification relies on factory or operator calibration of the assay response (i.e., signal) using reference standards (i.e., calibrators)

comprising known concentrations of analyte. The molecular counting device, by contrast, is designed to bind essentially every analyte molecule in a nanoscale sample volume. The number of analyte molecules is counted by detecting a first signal corresponding to the number of multimolecular sensors (i.e., tethered recognition devices) in the stimulated state and a second signal corresponding to the number of multimolecular sensors in the basal state.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/91.2

22. Document ID: US 6277576 B1

L23: Entry 22 of 94 File: USPT Aug 21, 2001

US-PAT-NO: 6277576
DOCUMENT-IDENTIFIER: US 6277576 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 22 of 94 File: USPT Aug 21, 2001

US-PAT-NO: 6277576
DOCUMENT-IDENTIFIER: US 6277576 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: August 21, 2001

US-CL-CURRENT: 435/6; 536/23.1, 536/24.3

APPL-NO: 9/ 306768
DATE FILED: May 7, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This is a continuing application of U.S. Ser. No. 08/873,598, filed Jun. 12, 1997, now U.S. Pat. No. 5,952,172 which is a continuing application of U.S. Ser. No. 08/660,534, filed Jun. 7, 1996, now U.S. Pat. No. 5,770,369, a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995, now U.S. Pat. No. 5,824,473, which is a continuing applicaiton of U.S. Ser. No. 08/166,036, filed Dec. 10, 1993 now U.S. Pat. No. 5,591,578.

L23: Entry 22 of 94 File: USPT Aug 21, 2001

DOCUMENT-IDENTIFIER: US 6277576 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

23. Document ID: US 6277489 B1

L23: Entry 23 of 94 File: USPT Aug 21, 2001

US-PAT-NO: 6277489
DOCUMENT-IDENTIFIER: US 6277489 B1

TITLE: Support for high performance affinity chromatography and other uses

L23: Entry 23 of 94 File: USPT Aug 21, 2001

US-PAT-NO: 6277489
DOCUMENT-IDENTIFIER: US 6277489 B1

TITLE: Support for high performance affinity chromatography and other uses

DATE-ISSUED: August 21, 2001

US-CL-CURRENT: 428/403; 427/217, 427/220, 428/404, 428/407, 428/450, 428/457, 428/699, 428/701, 428/702, 435/287.1, 435/287.2, 435/287.9, 435/7.1, 435/7.7, 435/7.8

APPL-NO: 9/ 205750
DATE FILED: December 4, 1998

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
This application is related to U.S. patent application Ser. No. 09/206,084, filed on an even day herewith (Dec. 4, 1998), the teachings of which are incorporated herein by reference for all purposes.

L23: Entry 23 of 94 File: USPT Aug 21, 2001

DOCUMENT-IDENTIFIER: US 6277489 B1
TITLE: Support for high performance affinity chromatography and other uses

Brief Summary Paragraph Right (1):
Self-assembled monolayers formed by the chemisorption of alkanethiols on gold are likely to now be the most intensively characterized synthetic organic monolayers prepared to date. See, Ulman, AN INTRODUCTION TO ULTRATHIN ORGANIC FILMS: FROM LANGMUIR-BLODGETT TO SELF ASSEMBLY, Academic Press, San Diego, 1991; Dubois el al., Annu. Rev. Phys. Chem., 43: 437 (1992). These monolayers form spontaneously during immersion of evaporated films of gold in solutions of alkanethiols as a result of chemisorption of sulfur on the (111) textured surface of the films. The molecules self-organize into a commensurate 3.times.3R30.degree. lattice on the surface of the Au(111). See, Porter, J. Am. Chem. Soc., 109: 3559 (1987); Camillone III, et al., Chem. Phys., 98: 3503 (1993); Fenter et al., Science, 266: 1216 (1994); 20; Chidsey et al., Langmuir, 6: 682 (1990); Sun etal., Thin Solid Films, 242: 106 (1994). For monolayers formed from CH.sub.3 (CH.sub.2).sub.n SH, n>9, at least, the aliphatic chains of the monolayers are extended in the all-trans conformation and tilted approximately 30.degree. from the normal of the surface. Because the spacing between sulfur groups on the 3.times.3R30.degree. lattice is, on average, 4.9 .ANG., whereas the van der Waals diameter of an aliphatic chains is only .about.4 .ANG., the aliphatic chains within these SAMs tilt from the normal so as to come into van der Waals contact and thereby maximize their cohesive dispersive interactions. Studies of the lateral structure within monolayers using X-ray diffraction reveal the existence of domains of size .about.100 .ANG., where each domain has one of six different tilt directions relative to the Au(111) face. See, Fenter et al., Science, 266: 1216 (1994). Recent studies have shown the existence a c(4.times.2) superlattice, the cause of which remains unresolved.

Brief Summary Paragraph Right (2):
Self-assembled monolayers formed with .omega.-substituted alkanethiols on the surface of gold have been used as model surfaces in a number of past studies of the interactions of proteins with surfaces (Spinke et al., Langumuir, 9: 1821 (1993); Willner et al., J. Am. Chem. Soc., 114: 10965 (1992); Song et al., J. Phys, Chem., 97: 6564 (1993); Mrksich et al., J. Am. Chem. Soc., 117: 12009 (1995)). For example, multilayer systems based on biotinylated alkanethiols and streptavidin have been used in schemes for the immobilization of Fab fragments of antibodies on surfaces (Spinke et al, Langumuir, 9: 1821 (1993)), and SAMs formed from NHS-activated disulfides have been used to form enzyme-based electrodes by covalent immobilization of glutathione reductase (Willner et al., J. Am. Chem. Soc., 114: 10965 (1992)). Cytochrome c, when adsorbed to SAMs formed from mercaptoundecanoic acid, has also been shown to be active and to possess a formal potential nearly identical to that of cytochrome c bound to physiological membranes (Song et al., J. Phys, Chem., 97: 6564 (1993)).

Brief Summary Paragraph Right (4):
Surfaces prepared by the chemisorption of organosulflur compounds on evaporated films of gold are not limited to the alkanethiols. Self-assembled monolayers formed from perfluorinated organosulfur compounds have also been reported. See, Lenk et al., Langmuir, 10: 4610(1994); Drawhorn et al., J. Phys. Chem., 99: 16511 (1995). These surfaces, too, can be highly ordered, although, interestingly, the origin of the order within the monolayer is largely intramolecular and contrasts, therefore, to monolayers formed from alkanethiols (where the order largely reflects the cohesive intermolecular dispersion force). Steric interactions between adjacent fluorine atoms of a perfluorinated chain cause the chain to twists itself into a rigid, helical conformation. That is, an isolated perfluoro chain is stiff, as compared to an aliphatic chain. Because perfluorinated chains have larger cross-sectional areas than alkanethiols, monolayers formed on gold from perfluorinated thiols are not tilted from the normal to the same degree as alkanethiols. See, Drawhorn et al., J. Phys. Chem., 99: 16511 (1995). Estimates by IR studies place the tilt of the perfluorinated chains at 0.about.10.degree.. Because perfluorinated chains within SAMs on Au(111) are not tilted to the same degree as the alkanethiols, their surfaces are not expected to possess domains formed from regions of monolayer with different tilt directions (as occurs with monolayers formed from alkanethiols).

Brief Summary Paragraph Right (8):
Self assembled monolayers have been constructed on silica particles by a number of known methods, however, silica gel particles are a less than ideal substrate for a number of reasons.

Brief Summary Paragraph Right (11):
Thus, a method of preparing a particulate material having a substantially homogeneous, easily assembled organic layer that does not adventitiously and/or nonspecifically bind charged species would represent a significant advance in the art. Surprisingly, the present invention provides such particles, and methods of preparing and using these particles.

Detailed Description Paragraph Right (1):
SAM, self assembled monolayer.

Detailed Description Paragraph Right (54):
In a presently preferred embodiment, organic layer components which form self-assembled monolayers are used.

Detailed Description Paragraph Right (55):
In the discussion that follows, self-assembled monolayers are utilized as an exemplary organic layer. This use is not intended to be limiting. It will be understood that the various configurations of the self-assembled monolayers and their methods of synthesis, binding properties and other characteristics are equally applicable to each of the organic layers of use in the present invention.

Detailed Description Paragraph Right (56):
Self-assembled monolayers are generally depicted as an assembly of organized, closely packed linear molecules. There are two widely-used methods to deposit molecular monolayers on solid substrates: Langmuir-Blodgett transfer and self-assembly. Additional methods include techniques such as depositing a vapor of the monolayer precursor onto a substrate surface. Each of these methods is appropriate for use in practicing the present invention.

Detailed Description Paragraph Right (333):
FTIR spectra of self-assembled monolayers formed form 1-hexadecanethiol on electroless gold supported on glass microscope slides have been measured by Hou and coworkers (Hou, Z. et al., Langmuir 14:3287 (1998)). Vibrational bands corresponding to symmetric and asymmetric H-C-H stretching vibrations were found at 2850 cm.sup.-1 and 2918 cm.sup.-1, respectively, indicating that long-chain alkanethiols do form densely packed monolayers on electroless gold. Electrochemical methods of characterization as well as measurements of contact angles further support the conclusion that densely-packed SAMs can be formed on electroless gold prepared by using the procedure described above. For example, the fractional coverage of the surface of electroless gold by a SAM formed from 1-hexadecanethiol was estimated to be 99.98% by using cyclic voltammetry. Here we use the fact that densely-packed SAMs form on electroless gold to estimate the available surface area of electroless gold supported on silica gel.

Detailed Description Paragraph Right (334):
Self-assembled monolayers were formed on gold-coated silica gel by suspending the gel in ethanol containing 1 of 1-dodecanethiol for 12 hours. The extent of adsorption of the alkanethiol from solution was measured by difference analysis using Ellman's test (Dubrovsky, T. et al., submittedfor publication to Langmuir). In the presence of free sulfhydryl groups, Ellman's reagent, 5,5'-dithiobis(2-nitrobenzoic acid), is reduced to 5-sulfido-2-nitrobenzoate (TNB). The intense yellow color of TNB was quantified by measuring its absorbance at 412 nm (.epsilon..sub.412 =13,600 M.sup.-1 cm.sup.-1). By using this method, the surface area of gold on the silica gel that adsorbed 1-dodecanethiol was found to be 0.93-1.28 m.sup.2 /g (assuming 25 .ANG..sup.2 /molecule within the SAM (Ulman, A. An Introduction to Ultrathin Organic Films: From Langmuir-Blodgett to Self-Assembly, Academic Press, Boston (1991)). The smaller specific surface area of the gold-coated silica gel as compared to bare silica gel (300-500 m.sup.2 /g) is consistent with our expectation that the gold plugs many of the pores of the gel. Although relatively small, we note that the specific surface area of the gold-coated gel is, in fact, sufficiently large to permit routine measurement of a change in bulk concentration of analyte released into solution from the surface of the gel (e.g., pNA). We also point out that gold-coated silica gel has a specific surface area that is higher than commercially available gold particles with diameters ranging between 2 and 8 .mu.m (0.24 to 0.349 m.sup.2 /g by adsorption of 1-dodecanethiol).

Detailed Description Paragraph Right (335):
Self-assembled monolayers formed from HO(CH.sub.2).sub.11 SH and HOOC(CH.sub.2).sub.11 SH lead to surface concentrations of carboxyl or hydroxyl group that range between 5-6 .mu.mol/m.sup.2. With large and bulky terminal groups, however, as with the tetrapeptide AAPF-pNA, such high densities of packing are not possible. By using base

(200 mM NaOH) to hydrolyze pNA from SAMs formed from pNA-FPAA-suc-(CH.sub.2)11SH on the surface of electroless gold, the surface density of AAPF-pNA was determined to be 2.6 .mu.mol/m.sup.2. This areal density is consistent with the cross-sectional area of AAPF (.about.60 .ANG..sup.2 /molecule).

Detailed Description Paragraph Center (10):
C.1 Self-Assembled Monolayers ("SAMs")

Current US Cross Reference Classification (10):
435/287.1

Current US Cross Reference Classification (11):
435/287.2

Current US Cross Reference Classification (12):
435/287.9

Current US Cross Reference Classification (13):
435/7.1

Current US Cross Reference Classification (14):
435/7.7

Current US Cross Reference Classification (15):
435/7.8

Other Reference Publication (2):
Lenk et al., "Structural Investigation of Molecular Organization in Self-Assembled Monolayers of a Semifluorinated Amidethiol" Langmuir 10:4610-4617 (1994).

Other Reference Publication (3):
Drawhorn et al., "Anchoring of Nematic Liquid Crystals on Self-Assembled Monolayers Formed from Alkanethiols on Semitransparent Films of Gold" J. Phys. Chem. 99:16511 (1995).

Other Reference Publication (7):
Grabar et al., "Nanoscale Characterization of Gold Colloid Monolayers: A Comparison of Four Techniques" Anal. Chem. 69:471-477 (1997).

Other Reference Publication (18):
Hou, Z. et al., "Electroless Gold as a Substrate for Self-Assembled Monolayers" Langmuir 14:3287-3297 (1998).

24. Document ID: US 6274320 B1

L23: Entry 24 of 94 File: USPT Aug 14, 2001

US-PAT-NO: 6274320
DOCUMENT-IDENTIFIER: US 6274320 B1

TITLE: Method of sequencing a nucleic acid

L23: Entry 24 of 94 File: USPT Aug 14, 2001

US-PAT-NO: 6274320
DOCUMENT-IDENTIFIER: US 6274320 B1

TITLE: Method of sequencing a nucleic acid

DATE-ISSUED: August 14, 2001

US-CL-CURRENT: 435/6; 435/287.2, 435/91.2

APPL-NO: 9/ 398833
DATE FILED: September 16, 1999
L23: Entry 24 of 94 File: USPT Aug 14, 2001

DOCUMENT-IDENTIFIER: US 6274320 B1
TITLE: Method of sequencing a nucleic acid

Detailed Description Paragraph Right (19):
Alternatively, the anchor primer can be attached to the solid support with a biotin derivative possessing a photo-removable protecting group. This moiety is covalently bound to bovine serum albumin (BSA), which is attached to the solid support, e.g., a glass surface. See Pirrung and Huang, 1996. Bioconjugate Chem. 7: 317-321. A mask is then used to create activated biotin within the defined irradiated areas. Avidin may then be localized to the irradiated area, with biotinylated DNA subsequently attached through a BSA-biotin-avidin-biotin link. If desired, an intermediate layer of silane is deposited in a self-assembled monolayer on a silicon dioxide silane surface that can be patterned to localize BSA binding in defined regions. See e.g., Mooney, et al., 1996. Proc. Natl. Acad. Sci. USA 93: 12287-12291.

Detailed Description Paragraph Right (75):
The photons generated by luciferase may be quantitated using a variety of detection apparatuses, e.g., a photomultiplier tube, charge-coupled display (CCD), absorbance photometer, and a luminometer, as well as the apparatuses described herein. In a preferred embodiment, the quantitation of the emitted photons is accomplished by the use of charge-coupled display (CCD) camera fitted with a microchannel plate intensifier. CCD detectors are described in, e.g., Bronks, et al., 1995. Anal. Chem. 65: 2750-2757. Preferably, the CCD camera uses a custom designed and fabricated CCD possessing a total of 16 million pixels (i.e., 4,000.times.4,000 pixel array) which can detect approximately 1% of the photons produced and can convert 40% to 80% of the photons produced into an actual measurable signal. With this system, approximately 1% of the photons produced are detected. This system can convert 40% to 80% of the photons produced into an actual measurable signal. Additionally, this CCD system possesses a minimum signal-to-noise ratio of 5:1, with a 10:1 signal-to-noise ratio being preferable.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/287.2

Current US Cross Reference Classification (2):
435/91.2

Other Reference Publication (54):
Service, "Microchip Arrays Put DNA on the Spot." Science 282(5388).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

25. Document ID: US 6268150 B1
L23: Entry 25 of 94 File: USPT Jul 31, 2001

US-PAT-NO: 6268150
DOCUMENT-IDENTIFIER: US 6268150 B1

TITLE: Nucleic acid mediated electron transfer
L23: Entry 25 of 94 File: USPT Jul 31, 2001

US-PAT-NO: 6268150
DOCUMENT-IDENTIFIER: US 6268150 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: July 31, 2001

US-CL-CURRENT: 435/6; 536/23.1, 536/24.3

APPL-NO: 9/ 459751
DATE FILED: December 10, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This application is a continuing application of U.S. Ser. No. 09/306,749, filed May 7, 1999, which is a continuing application of 08/873,598, filed Jun. 12, 1997, now U.S. Pat. No. 5,952,172, which is a continuing application of U.S. Ser. No. 08/660,534, filed Jun. 7, 1996, now U.S. Pat. No. 5,770,369, which is a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995, now U.S. Pat. No. 5,824,473, which is a continuing application of U.S. Ser. No. 08/166,036, filed Dec. 10, 1993, now U.S. Pat. No. 5,591,578.

L23: Entry 25 of 94 File: USPT Jul 31, 2001

DOCUMENT-IDENTIFIER: US 6268150 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films" Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayer of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemical Acta., 36(11/12):1799-1801 (1991).

26. Document ID: US 6268149 B1

L23: Entry 26 of 94 File: USPT Jul 31, 2001

US-PAT-NO: 6268149
DOCUMENT-IDENTIFIER: US 6268149 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 26 of 94 File: USPT Jul 31, 2001

US-PAT-NO: 6268149
DOCUMENT-IDENTIFIER: US 6268149 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: July 31, 2001

US-CL-CURRENT: 435/6; 435/287.2, 435/288.7, 536/23.1, 536/24.3

APPL-NO: 9/ 454498
DATE FILED: December 6, 1999

PARENT-CASE:

This application is a continuing application of U.S. Ser. No. 08/946,679, filed Oct. 8, 1997, U.S. Pat No. 6,087,100, which is a continuing application of Ser. No. 08/709,263 filed Sep. 6, 1996, U.S. Pat. No. 5,780,234, which is a continuing application of Ser. No. 08/166,036, filed Dec. 10, 1993, U.S. Pat. No. 5,591,578.

L23: Entry 26 of 94 File: USPT Jul 31, 2001

DOCUMENT-IDENTIFIER: US 6268149 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/287.2

Current US Cross Reference Classification (2):
435/288.7

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

27. Document ID: US 6265155 B1

L23: Entry 27 of 94 File: USPT Jul 24, 2001

US-PAT-NO: 6265155
DOCUMENT-IDENTIFIER: US 6265155 B1

TITLE: Metallic solid supports modified with nucleic acids

L23: Entry 27 of 94 File: USPT Jul 24, 2001

US-PAT-NO: 6265155
DOCUMENT-IDENTIFIER: US 6265155 B1

TITLE: Metallic solid supports modified with nucleic acids

DATE-ISSUED: July 24, 2001

US-CL-CURRENT: 435/6

APPL-NO: 8/ 808750
DATE FILED: February 28, 1997

PARENT-CASE:

This application is a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995 now U.S. Pat No. 5,824,473.

L23: Entry 27 of 94 File: USPT Jul 24, 2001

DOCUMENT-IDENTIFIER: US 6265155 B1
TITLE: Metallic solid supports modified with nucleic acids

Brief Summary Paragraph Right (60):
In a preferred embodiment, the blocking moieties, together with the modified nucleic acids, form a monolayer (sometimes referred to as a self-assembled monolayer (SAM)), as is generally understood by those in the art. The formation of a monolayer may be determined in several ways, as is appreciated by those in the art The presence of a monolayer on at least a portion of the surface may be determined as is known in the art, for example by using ellipsometry, X-ray photoelectron spectroscopy, infrared external reflectance spectroscopy, or surface plasmon resonance.

Detailed Description Paragraph Right (4):

A self-assembled monolayer of modified nucleic acids and C.sub.6 blocking moieties with hydroxyl terminal groups was made.

Detailed Description Paragraph Right (14):
Samples that were hybridized with oligomer complementary with the one attached to the surface showed more than 10 times higher activity level than samples that were reacted with a non-complementary oligomer. Gold surfaces coated with HS--(CH.sub.2).sub.16 --OH monolayer, in the absence of nucleic acid, and reacted with either LS or LT did not show significant counts above the background activity. Therefore, the formation of a mixed self-assembled monolayer resulted in covalent attachment of DNA strands to the surface without significant losses in binding activity and specificity.

Current US Original Classification (1):
435/6

Other Reference Publication (18):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (19):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (72):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (77):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (82):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (89):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (93):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

CLAIMS:

1. An array of nucleic acids comprising a solid support having at plurality of regions, each region comprising a metallic surface comprising a self-assembled mixed monolayer comprising:

a) blocking moieties, having at least a first end attached to said metallic surface and at least a second end comprising a terminal group, wherein said blocking moieties shield nucleic acids from said metallic surface; and

b) at least one modified nucleic acid, comprising a nucleic acid and a linker moeity having a first and second end, wherein said first end of said linker is attached to said metallic surface and said second end is attached to said nucleic acid;

wherein at least two different regions comprise different nucleic acids.

15. A method of hybridizing a probe nucleic acid to a target nuclici acid, said method comprising adding a target nucleic acid to an array of probe nucleic acids comprising a solid support having at plurality of regions, each region comprising a metallic surface comprising a self-assembled mixed monolayer comprising:

a) blocking moieties, having at least a first end attached to said metallic surface and

at least a second end comprising a tenninal group, wherein said blocking moieties shield nucleic acids from said metallic surface; and

b) at least one modified nucleic acid, comprising a probe nucleic acid and a linker moeity having a first and second end, wherein said first end of said linker is attached to said solid support and said second end is attached to said nucleic acid;

wherein at least two different regions comprise different probe nucleic acids; under conditions wherein at least one of said probe nucleic acids and said target nucleic acid will hybridize to form a hybridization complex.

28. Document ID: US 6264893 B1

L23: Entry 28 of 94 File: USPT Jul 24, 2001

US-PAT-NO: 6264893
DOCUMENT-IDENTIFIER: US 6264893 B1

TITLE: Method and apparatus for developing thin layer chromatography plates for maximizing mobile phase conditions in column chromatography

L23: Entry 28 of 94 File: USPT Jul 24, 2001

US-PAT-NO: 6264893
DOCUMENT-IDENTIFIER: US 6264893 B1

TITLE: Method and apparatus for developing thin layer chromatography plates for maximizing mobile phase conditions in column chromatography

DATE-ISSUED: July 24, 2001

US-CL-CURRENT: 422/70; 210/198.3, 422/102, 422/104, 436/162, 73/61.54

APPL-NO: 9/ 290215
DATE FILED: April 13, 1999

PARENT-CASE:

This application claim benefit to provisional application No. 60/081,457 Apr. 13, 1998.

L23: Entry 28 of 94 File: USPT Jul 24, 2001

DOCUMENT-IDENTIFIER: US 6264893 B1
TITLE: Method and apparatus for developing thin layer chromatography plates for maximizing mobile phase conditions in column chromatography

Brief Summary Paragraph Right (2):
The invention relates to an apparatus and method for improving the speed and efficiency in performing thin layer chromatography (TLC) tests. Thin layer chromatography, one of the most standard laboratory techniques, is a solid-liquid partitioning technique used in chemical analysis. It is a micro-scale technique since only micrograms of material are needed to perform the analysis. A thin layer chromatography plate consists of a thin layer of adsorbent material (stationary phase) coated on a backing support. Typically, the support is, but is not limited to, a glass plate and the adsorbent material is, but is not limited to, a silica/silicate material. When the thin layer plate is partially submerged in a liquid (mobile phase), the liquid ascends the adsorbent by capillary action. By placing a small spot of a solution containing two

compounds near the base of the thin layer plate, yet not immersed in the solvent, the ascending liquid carries the sample and partitions the sample between the adsorbent stationary phase and the liquid mobile phase (commonly referred to as developing). After development, the plate can be visualized and the distance a given compound travels with respect to the distance the solvent travels is referred to as the compounds Rf value and is expressed as a ratio. The Rf value is determined by a number of factors, namely the chemical structure of the compound and its interactions with the prescribed stationary and mobile phases. Changing the composition of either the stationary phase compound or mobile phase solvent can have dramatic effects on not only how far the sample travels with respect to the solvent front (Rf), but how tightly the compound travels together (the spot size and shape).

Current US Original Classification (1):
422/70

Current US Cross Reference Classification (2):
422/102

Current US Cross Reference Classification (3):
422/104

Current US Cross Reference Classification (4):
436/162

Other Reference Publication (2):
Pavia et al., Organic Laboratory Techniques, A Microscale Approach, Saunders College Publishing, Philadelphia, Chapters 12-13, pp. 696-737 (1990).

CLAIMS:

20. A thin layer chromatography assembly, comprising

means fining a chamber having an open upper end and receivable of a chromatographic fluid,

a plunger block for closing said upper end of said chamber,

a movable plunger coupled to said plunger block, said plunger having an accessible portion exterior of said chamber and including a shaft extending through said plunger block, an end of said shaft being positionable in said chamber,

a plate holding clip arranged at said end of said shaft, said end of said shaft being connected to said plate holding clip, and

a thin layer chromatography plate retained by said plate holding clip.

27. A thin layer chromatography assembly, comprising

means defining a chamber having an open upper end and receivable of a chromatographic fluid,

a plunger block for closing said upper end of said chamber,

a movable plunger coupled to said plunger block and having a first accessible end exterior of said chamber and a second end positionable in said chamber,

a plate holding frame coupled to said second end of said plunger, said plate holding frame having opposed, upturned edges, and

a thin layer chromatography plate retained between said upturned edges of said plate holding frame.

29. Document ID: US 6258545 B1

L23: Entry 29 of 94 File: USPT Jul 10, 2001

US-PAT-NO: 6258545
DOCUMENT-IDENTIFIER: US 6258545 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 29 of 94 File: USPT Jul 10, 2001

US-PAT-NO: 6258545
DOCUMENT-IDENTIFIER: US 6258545 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: July 10, 2001

US-CL-CURRENT: 435/6; 435/194, 435/287.2, 435/91.2, 536/23.1, 536/24.3, 536/24.33

APPL-NO: 9/ 545227
DATE FILED: April 7, 2000

PARENT-CASE:

The instant application, Ser. No. 09/545,227, filed Apr. 7, 2000, is a continuing application of Ser. No. 09/100,507, filed on Jun. 19, 1998, now U.S. Pat. No. 6,071,699, which is a continuing application of Ser. No. 08/660,534 filed Jan. 7, 1996, now U.S. Pat. No. 5,770,369, which is a continuing application of Ser. No. 08/475,051 filed Jun. 7, 1995, now U.S. Pat. No. 5,824,473; which is a continuing application of Ser. No. 08/166,036, filed Dec. 10, 1993, now U.S. Pat. No. 5,591,578.

L23: Entry 29 of 94 File: USPT Jul 10, 2001

DOCUMENT-IDENTIFIER: US 6258545 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/194

Current US Cross Reference Classification (2):
435/287.2

Current US Cross Reference Classification (3):
435/91.2

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta, 36(11/12):1799-1801 (1991).

30. Document ID: US 6251691 B1

L23: Entry 30 of 94 File: USPT Jun 26, 2001

US-PAT-NO: 6251691
DOCUMENT-IDENTIFIER: US 6251691 B1

TITLE: Light-controlled electrokinetic assembly of particles near surfaces

L23: Entry 30 of 94 File: USPT Jun 26, 2001

US-PAT-NO: 6251691
DOCUMENT-IDENTIFIER: US 6251691 B1

TITLE: Light-controlled electrokinetic assembly of particles near surfaces

DATE-ISSUED: June 26, 2001

US-CL-CURRENT: 436/534; 204/400, 204/414, 204/415, 204/416, 204/417, 422/129, 422/131, 422/138, 422/186, 422/186.04, 422/186.05, 422/186.13, 422/50, 422/54, 422/55, 422/56, 422/57, 422/58, 422/68.1, 422/69, 422/82.01, 422/82.02, 422/82.03, 422/82.05, 422/82.06, 422/82.09, 435/173.1, 435/174, 435/176, 435/177, 435/283.1, 435/287.1, 435/288.7, 435/289.1, 435/290.1, 435/6, 435/808, 435/810, 435/814, 435/90, 435/91.2, 435/91.5 , 435/91.51, 436/164, 436/165, 436/166, 436/169, 436/172, 436/175, 436/501, 436/518, 436/524, 436/526, 436/528, 436/531, 436/535, 436/63

APPL-NO: 9/ 171550
DATE FILED: October 26, 1998

PARENT-CASE:

This application is a 35 U.S.C..sctn.371 application of PCT International Application No. PCT/U.S. Pat. No. 97/081,59, filed Apr. 24, 1997, which in turn claims priority of U.S. Provisional Application No. 60/016,642, filed Apr. 25, 1996.

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/US97/08159	April 24, 1997	WO97/40385	Oct 30, 1997	Oct 26, 1998	Oct 26, 1998

L23: Entry 30 of 94 File: USPT Jun 26, 2001

DOCUMENT-IDENTIFIER: US 6251691 B1
TITLE: Light-controlled electrokinetic assembly of particles near surfaces

Detailed Description Paragraph Right (44):
Colloidal particulates have been previously employed in flat-panel display technology. The operating principle of these designs is based on electrophoretic motion of pigments in a colored fluid confined between two planar electrodes. In the OFF (dark) state, pigments are suspended in the fluid, and the color of the fluid defines the appearance of the display in that state. To attain the ON (bright) state, particles are assembled near the front (transparent) electrode under the action of an electric field. In this latter state, incident light is reflected by the layer of particles assembled near the electrode, and the display appears bright. Prototype displays employing small reflective particles in accordance with this design are known. However, these displays suffered from a number of serious problems including: electrochemical degradation and lack of colloidal stability as a result of prolonged exposure to the high DC electric fields required to achieve acceptable switching speeds; and non-uniformities introduced by particle migration in response to field gradients inherent in the design of the addressing scheme.

Detailed Description Paragraph Right (59):
The present invention of forming heterogeneous panels requires the chemical attachment of target ligands to beads. Ligands may be coupled to beads "off-line" by a variety of well established coupling reactions. For present purposes, the bead identity must be chemically encoded so it may be determined as needed. Several methods of encoding, or binary encoding, of beads are available. For example, short oligonucleotides may serve the purpose of identifying a bead via their sequence which may be determined by microscale sequencing techniques. Alternatively, chemically inert molecular tags may be employed that are readily identified by standard analytical techniques.

Detailed Description Paragraph Right (103):
Several methods of encoding, or binary encoding, of beads are available. Two examples are as follows. First, beads may be labeled with short oligonucleotides such as the 17-mers typically employed in hybridization experiments. The sequence of such short probes may be determined by microscale sequencing techniques such as direct Maxam-Gilbert sequencing or mass spectrometry. This encoding scheme is suitable when the task calls for screening of libraries of nucleic acid ligands or oligopeptides. Second, members of a combinatorial library may be associated with chemically inert molecular tags. In contrast to the previous case, these tag molecules are not sequentially linked. Instead, the sequence of reaction steps is encoded by the formal assignment of a binary code to individual tag molecules and their mixtures that are attached to the bead in each successive reaction step. The tags are readily identified by standard analytical techniques such as gas chromatography. This general encoding strategy is currently employed in the synthesis of combinatorial libraries on colloidal beads.

Current US Original Classification (1):
436/534

Current US Cross Reference Classification (1):
204/400

Current US Cross Reference Classification (2):
204/414

Current US Cross Reference Classification (3):
204/415

Current US Cross Reference Classification (4):
204/416

Current US Cross Reference Classification (5):
204/417

Current US Cross Reference Classification (6):
422/129

Current US Cross Reference Classification (7):
422/131

Current US Cross Reference Classification (8):

422/138

Current US Cross Reference Classification (9):
422/186

Current US Cross Reference Classification (10):
422/186.04

Current US Cross Reference Classification (11):
422/186.05

Current US Cross Reference Classification (12):
422/186.13

Current US Cross Reference Classification (13):
422/50

Current US Cross Reference Classification (14):
422/54

Current US Cross Reference Classification (15):
422/55

Current US Cross Reference Classification (16):
422/56

Current US Cross Reference Classification (17):
422/57

Current US Cross Reference Classification (18):
422/58

Current US Cross Reference Classification (19):
422/68.1

Current US Cross Reference Classification (20):
422/69

Current US Cross Reference Classification (21):
422/82.01

Current US Cross Reference Classification (22):
422/82.02

Current US Cross Reference Classification (23):
422/82.03

Current US Cross Reference Classification (24):
422/82.05

Current US Cross Reference Classification (25):
422/82.06

Current US Cross Reference Classification (26):
422/82.09

Current US Cross Reference Classification (27):
435/173.1

Current US Cross Reference Classification (28):
435/174

Current US Cross Reference Classification (29):
435/176

Current US Cross Reference Classification (30):
435/177

Current US Cross Reference Classification (31):

435/283.1

Current US Cross Reference Classification (32):
435/287.1

Current US Cross Reference Classification (33):
435/288.7

Current US Cross Reference Classification (34):
435/289.1

Current US Cross Reference Classification (35):
435/290.1

Current US Cross Reference Classification (36):
435/6

Current US Cross Reference Classification (37):
435/808

Current US Cross Reference Classification (38):
435/810

Current US Cross Reference Classification (39):
435/814

Current US Cross Reference Classification (40):
435/90

Current US Cross Reference Classification (41):
435/91.2

Current US Cross Reference Classification (42):
435/91.5

Current US Cross Reference Classification (43):
435/91.51

Current US Cross Reference Classification (44):
436/164

Current US Cross Reference Classification (45):
436/165

Current US Cross Reference Classification (46):
436/166

Current US Cross Reference Classification (47):
436/169

Current US Cross Reference Classification (48):
436/172

Current US Cross Reference Classification (49):
436/175

Current US Cross Reference Classification (50):
436/501

Current US Cross Reference Classification (51):
436/518

Current US Cross Reference Classification (52):
436/524

Current US Cross Reference Classification (53):
436/526

Current US Cross Reference Classification (54):

436/528

Current US Cross Reference Classification (55):
436/531

Current US Cross Reference Classification (56):
436/535

Current US Cross Reference Classification (57):
436/63

31. Document ID: US 6251343 B1

L23: Entry 31 of 94 File: USPT Jun 26, 2001

US-PAT-NO: 6251343
DOCUMENT-IDENTIFIER: US 6251343 B1

TITLE: Microfluidic devices and systems incorporating cover layers

L23: Entry 31 of 94 File: USPT Jun 26, 2001

US-PAT-NO: 6251343
DOCUMENT-IDENTIFIER: US 6251343 B1

TITLE: Microfluidic devices and systems incorporating cover layers

DATE-ISSUED: June 26, 2001

US-CL-CURRENT: 422/102; 422/100, 422/103, 422/104, 422/68.1, 422/99, 436/174, 436/179, 436/180, 73/863, 73/863.01, 73/863.71

APPL-NO: 9/ 028965
DATE FILED: February 24, 1998

L23: Entry 31 of 94 File: USPT Jun 26, 2001

DOCUMENT-IDENTIFIER: US 6251343 B1
TITLE: Microfluidic devices and systems incorporating cover layers

Abstract Paragraph Left (1):
The present invention provides microfluidic devices that comprise a body structure comprising at least a first microscale channel network disposed therein. The body structure has a plurality of ports disposed in the body structure, where each port is in fluid communication with one or more channels in the first channel network. The devices also include a cover layer comprising a plurality of apertures disposed through the cover layer. The cover layer is mated with the body structure whereby each of the apertures is aligned with a separate one of the plurality of ports.

Brief Summary Paragraph Right (1):
As has been the case in the electronics and computer industries, trends in analytical chemical and biochemical instrumentation have been toward miniaturization. In chemical and biochemical analyses, such miniaturization as achieved in e.g., microfluidic systems, provides numerous advantages, including significantly smaller reagent requirements, faster throughput, ready automatability, and in many cases, improved data.

Brief Summary Paragraph Right (2):
By way of example, U.S. Pat. Nos. 5,498,392 and 5,587,128 describe the performance of

amplification reactions in microfabricated devices including microscale flow systems and/or reaction chambers. Such systems substantially reduce the requirements for expensive reagents utilized in amplification reactions. Further, the small scale of these devices also provides for enhanced thermal transfer between heating sources and the reagents in the device.

Brief Summary Paragraph Right (4):
Commonly owned Published International Application No. WO 98/00231 describes the use of microfluidic devices and systems in the performance of high-throughput screening assays. Again, these systems reduce the required volumes of potentially very expensive test compounds, e.g., drug candidates, library compounds, etc.

Brief Summary Paragraph Right (6):
It would therefore be desirable to provide microfluidic devices that capture the advantages associated with extremely small volumes and dimensions, without the problems associated with such small-scale devices. The present invention meets these and a variety of other needs.

Brief Summary Paragraph Right (7):
It is a general object of the present invention to provide microfluidic devices that combine the advantages of microfluidics with improved material handling characteristics and reduced costs for manufacturing. The present invention accomplishes this in a first aspect, by providing microfluidic devices that incorporate a body structure comprising at least a first microscale channel network disposed therein. The body structure has a plurality of ports disposed in it, where each port is in fluid communication with one or more channels in the first channel network. The devices also include a cover layer comprising a plurality of apertures disposed therethrough. The cover layer is mated with the body structure whereby each of the apertures is aligned with a separate one of the plurality of ports.

Brief Summary Paragraph Right (9):
In a related aspect, the present invention provides a microfluidic system that includes a microfluidic device in accordance with the present invention, where the device is further mounted on a controller/detector apparatus that is configured to receive the microfluidic device. The controller/detector apparatus comprises an optical detection system and a material transport system, where the detection system and transport system are operably interfaced with the microfluidic device when the device is mounted on the controller/detector.

Drawing Description Paragraph Right (1):
FIG. 1 schematically illustrates a microfluidic device body structure that incorporates a planar layered structure.

Drawing Description Paragraph Right (2):
FIGS. 2A-E illustrate from a number of perspectivesan embodiment of a cover layer for incorporation in a microfluidic device in accordance with the present invention.

Drawing Description Paragraph Right (3):
FIG. 2F illustrates the interaction of a filling device with the microfluidic devices of the invention.

Drawing Description Paragraph Right (4):
FIG. 3A illustrates a fully assembled microfluidic device that includes the layered body structure of FIG. 1 and the cover layer of FIG. 2 mated together.

Drawing Description Paragraph Right (5):
FIG. 3B illustrates an alternate mechanism for joining the body structure to the cover layer in the fully assembled device.

Detailed Description Paragraph Right (1):
The present invention generally provides microfluidic devices that take advantage of the extremely small-scale nature of microfluidic devices and systems, while at the same time, not suffering from some of the potential problems associated with such systems. In particular, the microfluidic devices and systems of the invention include an additional cover layer as a portion of the microfluidic device, e.g., overlaying and attached to the basic body structure of the device. The cover layer employed in the devices of the invention typically comprises a number of apertures disposed through it, which apertures mate with and/or form part of the reservoirs and/or access ports of the microfluidic device. These cover layers provide a number of advantages in the operation

and fabrication of microfluidic devices.

Detailed Description Paragraph Right (2):
As used herein, the terms "microscale," "microfabricated" or "microfluidic" generally refer to one or more fluid passages, chambers or conduits which have at least one internal cross-sectional dimension, e.g., depth, width, length, diameter, etc., that is less than 500 .mu.m, and typically between about 0.1 .mu.m and about 500 .mu.m. In the devices of the present invention, the microscale channels or chambers preferably have at least one cross-sectional dimension between about 0.1 .mu.m and 200 .mu.m, more preferably between about 0.1 .mu.m and 100 .mu.m, and often between about 0.1 .mu.m and 20 .mu.m. Accordingly, the microfluidic devices or systems prepared in accordance with the present invention typically include at least one microscale channel, usually at least two intersecting microscale channels, and often, three or more intersecting channels disposed within a single body structure. Channel intersections may exist in a number of formats, including cross intersections, "T" intersections, or any number of other structures whereby at least two channels are in fluid communication.

Detailed Description Paragraph Right (3):
The body structure of the microfluidic devices described herein can take a variety of shapes and/or conformations, provided the body structure includes at least one microfluidic channel element disposed within it. For example, in some cases the body structure has a tubular conformation, e.g., as in capillary structures, such as fused silica or polymeric capillaries that include internal diameters in the microscale range, set forth above. Alternatively, body structures may incorporate non-uniform shapes and/or conformations, depending upon the application for which the device is to be used. In preferred aspects, the body structure of the microfluidic devices incorporates a planar or "chip" structure.

Detailed Description Paragraph Right (4):
Although in some cases, a single piece body structure, e.g., a capillary, may be used, the devices described herein typically comprise an aggregation of two or more separate layers which when appropriately mated or joined together, form the body structure of the microfluidic device of the invention, e.g., containing the channels and/or chambers described herein. Typically, the microfluidic devices described herein will comprise a top portion, a bottom portion, and an interior portion, wherein the interior portion substantially defines the channels and chambers of the device.

Detailed Description Paragraph Right (5):
FIG. 1 illustrates one example of the body structure of a microfluidic device that incorporates a planar, layered structure. As shown, the body structure 100 includes at least two layers, an upper layer 102 and a lower layer 110. The upper surface 112 of the lower layer 110 is fabricated to include grooves and/or wells 114. The lower surface 104 of the upper layer 102 is then mated to the upper surface 112 of the lower layer 110 such that the grooves and/or channels define channels or conduits, and chambers within the interior of the aggregate body structure.

Detailed Description Paragraph Right (6):
A variety of substrate materials may be employed as the bottom portion. Typically, because the devices are microfabricated, substrate materials will be selected based upon their compatibility with known microfabrication techniques, e.g., photolithography, wet chemical etching, laser ablation, reactive ion etching (RIE), air abrasion techniques, injection molding, LIGA methods, metal electroforming, embossing, and other techniques. Suitable substrate materials are also generally selected for their compatibility with the full range of conditions to which the microfluidic devices may be exposed, including extremes of pH, temperature, salt concentration, and application of electric fields. Accordingly, in some preferred aspects, the substrate material may include materials normally associated with the semiconductor industry in which such microfabrication techniques are regularly employed, including, e.g., silica based substrates, such as glass, quartz, silicon or polysilicon, as well as other substrate materials, such as gallium arsenide and the like. In the case of semiconductive materials, it will often be desirable to provide an insulating coating or layer, e.g., silicon oxide, over the substrate material, and particularly in those applications where electric fields are to be applied to the device or its contents. In preferred aspects, the substrates used to fabricate the bodystructure are silica-based, and more preferably glass or quartz, due to their inertness to the conditions described above, as well as the ease with which they are microfabricated.

Detailed Description Paragraph Right (7):
In alternate preferred aspects, the substrate materials comprise polymeric materials,

e.g., plastics, such as polymethylmethacrylate (PMMA), polycarbonate, polytetrafluoroethylene (TEFLON.TM.), polyvinylchloride (PVC), polydimethylsiloxane (PDMS), polysulfone, polystyrene, polymethylpentene, polypropylene, polyethylene, polyvinylidine fluoride, ABS (acrylonitrile-butadiene-styrene copolymer), and the like. Such polymeric substrates are readily manufactured using available microfabrication techniques, as described above, or from microfabricated masters, using well known molding techniques, such as injection molding, embossing or stamping, or by polymerizing the polymeric precursor material within the mold (See U.S. Pat. No. 5,512,131). Again, such polymeric substrate materials are preferred for their ease of manufacture, low cost and disposability, as well as their general inertness to most extreme reaction conditions. Again, these polymeric materials may include treated surfaces, e.g., derivatized or coated surfaces, to enhance their utility in the microfluidic system, e.g., provide enhanced fluid direction, e.g., as described in U.S. patent application Ser. No. 08/843,212, filed Apr. 14, 1997 now U.S. Pat. No. 5,885,470, and which is incorporated herein by reference in its entirety for all purposes.

Detailed Description Paragraph Right (9):
In many embodiments, the microfluidic devices include an optical detection window 116 disposed across one or more channels and/or chambers of the device. Optical detection windows are typically transparent such that they are capable of transmitting an optical signal from the channel/chamber over which they are disposed. Optical detection windows may merely be a region of a transparent layer of the body structure, e.g., where the layer is glass or quartz, or a transparent polymer material, e.g., PMMA, polycarbonate, etc. Alternatively, where opaque substrates are used in manufacturing the devices, transparent detection windows fabricated from the above materials may be separately manufactured into the device.

Detailed Description Paragraph Right (10):
Microfluidic devices may be used in a variety of applications, including, e.g., the performance of high throughput screening assays in drug discovery, immunoassays, diagnostics, genetic analysis, and the like. As such, the devices described herein, will often include multiple sample introduction ports or reservoirs, for the parallel or serial introduction and analysis of multiple samples. Alternatively, these devices may be coupled to a sample introduction port, e.g., a pipettor, which serially introduces multiple samples into the device for analysis. Examples of such sample introduction systems are described in e.g., U.S. patent application Ser. No. 08/761,575 now U.S. Pat. No. 6,046,056 and Ser. No. 08/760,446 now U.S. Pat. No. 5,880,071 each of which was filed on Dec. 6, 1996, and is hereby incorporated by reference in its entirety for all purposes.

Detailed Description Paragraph Right (11):
In preferred aspects, the microfluidic devices of the present invention utilize electrokinetic material transport systems to direct and transport materials through the channels of the device. As used herein, "electrokinetic material transport" generally refers to systems and methods for transporting and directing materials within an interconnected channel and/or chamber containing structure, through the application of electrical fields to the materials, thereby causing material movement through and among the channels and/or chambers, i.e., cations will move toward the negative electrode, while anions will move toward the positive electrode.

Detailed Description Paragraph Right (13):
"Controlled electrokinetic material transport and direction," as used herein, refers to electrokinetic systems as described above, which employ active control of the voltages applied at multiple, i.e., more than two, electrodes. Rephrased, such controlled electrokinetic systems concomitantly regulate voltage gradients applied across at least two intersecting channels. Controlled electrokinetic material transport is described in Published PCT Application No. WO 96/04547, to Ramsey, which is incorporated herein by reference in its entirety for all purposes. In particular, the preferred microfluidic devices and systems described herein, include a body structure which includes at least two intersecting channels or fluid conduits, e.g., interconnected, enclosed chambers, which channels include at least three unintersected termini. The intersection of two channels refers to a point at which two or more channels are in fluid communication with each other, and encompasses "T" intersections, cross intersections, "wagon wheel" intersections of multiple channels, or any other channel geometry where two or more channels are in such fluid communication. An unintersected terminus of a channel is a point at which a channel terminates not as a result of that channel's intersection with another channel, e.g., a "T" intersection. In preferred aspects, the devices will include at least three intersecting channels having at least four unintersected

termini. In a basic cross channel structure, where a single horizontal channel is intersected and crossed by a single vertical channel, controlled electrokinetic material transport operates to controllably direct material flow through the intersection, by providing constraining flows from the other channels at the intersection. For example, assuming one was desirous of transporting a first material through the horizontal channel, e.g., from left to right, across the intersection with the vertical channel. Simple electrokinetic material flow of this material across the intersection could be accomplished by applying a voltage gradient across the length of the horizontal channel, i.e., applying a first voltage to the left terminus of this channel, and a second, lower voltage to the right terminus of this channel, or by allowing the right terminus to float (applying no voltage). However, this type of material flow through the intersection would result in a substantial amount of diffusion at the intersection, resulting from both the natural diffusive properties of the material being transported in the medium used, as well as convective effects at the intersection.

Detailed Description Paragraph Right (18):
As noted previously, in the design and fabrication of microfluidic systems, and underlying goal is to miniaturize the entire system. This is typically done either to reduce volume, increase the speed of the operation, or multiplex the particular operation, e.g., incorporate multiple operations within the same unit space occupied by the device. In accomplishing these goals, however, the channel networks that effectively define the functional space of a given microfluidic system become much smaller. As a result of smaller channel networks, or more complex networks being incorporated into the same unit space, the access points for these channel networks, e.g., reservoirs, electrical access ports and the like, are drawn closer and closer together.

Detailed Description Paragraph Right (20):
In a similar problem, as access ports are placed closer together, it also becomes more difficult to isolate those ports electrically. This is of particular importance in microfluidic systems that utilize electrical systems operably coupled to the channel networks, such as in electrical sensing systems, e.g., amperometric, potentiometric, etc., and/or electrokinetic material transport that are used for transport of materials through the channel networks, as described above. In particular, where the ports of the system are used for electrical access, the possibility of bridging currents, or "shorts," between two or more adjacent or at least proximal electrodes increases, e.g., across the surface of the device as a result of fluids, dirt or oils deposited on the surface of the device.

Detailed Description Paragraph Right (21):
The present invention generally addresses these problems by providing microfluidic devices that include a cover layer that provides an effective barrier between neighboring reservoirs, to prevent fluid and/or electrical links from forming between neighboring electrodes. The barrier optionally includes a ridge around each of the reservoirs, e.g., an annular ridge surrounding a circular reservoir. The ridge has the effect of preventing fluid `spill-over` from one well entering into another adjacent well. Similarly, the ridge effectively creates a longer path length across which any electrical bridging current, e.g., short circuit, must travel. Typically, these ridges extend at least 0.1 mm from the surface of the cover layer, preferably, at least 1 mm and in some cases, at least 2 mm or more, from the upper surface of the cover layer. In many cases, the barrier, e.g., as provided by the ridge structure, will increase the effective path length between neighboring wells by at least 1.5.times., preferably at least 2.times., and often at least 3-5.times. over that provided by the reservoirs in the body structure, alone.

Detailed Description Paragraph Right (22):
The use of separate or integrated holding structures for microfluidic devices is described in commonly owned Provisional Patent Application No. 08/906,441, filed Aug. 5, 1997, and incorporated herein by reference in its entirety for all purposes.

Detailed Description Paragraph Right (24):
The cover layer component of the microfluidic devices of the present invention also provides the capability to increase the volume capacity of the reservoirs of those devices. In particular, the apertures disposed in the cover layer can increase the total depth of the fluid reservoirs of the device by extending those reservoirs. While fluid volume is not a critical limitation in many microfluidic applications, there are some instances where substantial variations in fluid volume from, e.g., evaporation, can have an effect on a particular operation. This is typically due to concentration of

one or more solutes within the fluids, e.g., salts, enzymes, etc. By increasing the fluid volume capacity of the reservoirs, one can substantially mitigate any effects resulting from a partial evaporation of fluids by reducing the percentage of evaporation.

Detailed Description Paragraph Right (26):
The cover layer aspect of the microfluidic devices described herein may generally be fabricated from any of a number of different materials using a number of different methods. For example, the materials and methods described above in the manufacture of the microfluidic elements of the device may also be employed in the manufacture of the cover layer. While these methods are effective, in preferred aspects, more conventional manufacturing techniques are used to produce the cover layer. In particular, because the cover layer does not need to be manufactured to the tolerances of the microfluidic elements of the devices of the invention, they can generally be manufactured using less precise and less expensive or time consuming methods and from less costly materials.

Detailed Description Paragraph Right (27):
For example, in a layered microfluidic device fabricated from two glass layers, fabrication of the ports or reservoirs in one layer, e.g., by drilling or air abrasion techniques, can take a substantial amount of time. Further, the amount of time required for such fabrication increases in a non-linear, e.g., exponential, fashion with increasing substrate thickness. Conversely, reduction of substrate thickness reduces the amount of time required to fabricate the reservoirs, in an exponential fashion. Because a portion of the volume of the reservoirs in the final microfluidic device is optionally supplied by the cover layer element, the substrate layers used to fabricate the body structure of microfluidic device can be substantially thinner. Specifically, less of the total desired volume of the reservoir is a function of substrate thickness. As a result, fabrication time and cost associated with the manufacturing of reservoirs in the body structure are substantially reduced.

Detailed Description Paragraph Right (28):
Typically, the cover layer comprises an injection molded polymeric or plastic part, fabricated from any of a number of different manufacturable plastics. For example, the cover layer is typically fabricated from any of the polymeric materials described above for fabricating the body structure of the microfluidic device, e.g., polymethylmethacrylate (PMMA), polycarbonate, polytetrafluoroethylene (TEFLON.TM.), polyvinylchloride (PVC), polydimethylsiloxane (PDMS), polysulfone, polystyrene, polymethylpentene, polypropylene, polyethylene, polyvinylidine fluoride, ABS, and the like. In alternate aspects, the cover layer is optionally fabricated from non-polymeric materials, e.g., silica-based substrates, such as glass, quartz, silicon, as well as ceramics or metals.

Detailed Description Paragraph Right (30):
In alternate aspects, the body structure is attached to the cover layer via a clamping mechanism. In such aspects, an optional flexible gasket, e.g., latex, silicone, etc., is placed between the upper surface of the body structure and the lower surface of the cover layer. The body structure is then compressively clamped against the cover layer forming a sealed, joined structure. Suitable clamping mechanisms may be separate from the body structure/cover layer assembly, i.e., screw clamps, clip-style clamps, e.g., that clamp the edges of the body structure and cover layer, and the like. Alternatively, integrated clamping mechanisms are provided as a portion of the cover layer, into which the body structure is snapped. Such clamping systems are described in greater detail below, with reference to FIG. 3B.

Detailed Description Paragraph Right (31):
One aspect of the cover layer used in conjunction with the microfluidic devices of the present invention is shown in FIG. 2, from the top (FIG. 2A), side (FIG. 2B), bottom (FIG. 2C), top perspective (FIG. 2D) and bottom perspective views (FIG. 2E). As shown, the cover layer 200 is planar in shape having an upper planar surface 202 and a lower planar surface 204. Also included are a plurality of apertures 206 disposed through the cover layer, e.g., from the upper to lower planar surfaces. Apertures 206 are positioned within the cover so as to align with ports/reservoirs in the body structure of a microfluidic device (e.g., as shown in FIG. 1) when that body structure is mated to the lower planar surface 204 of cover layer 200.

Detailed Description Paragraph Right (33):
As shown, an annular ridge 208 is provided on the upper surface 202 of the cover layer 200, surrounding each separate aperture 206. This ridge provides a barrier between neighboring reservoirs in the overall device and also functions to increase the

effective volume of each reservoir in the resulting device. In addition, the apertures 206 in the cover layer are optionally provided with tapered walls 210, which are wider at the upper surface and narrower at the lower surface. The tapered walls allow the apertures to perform a funnel-like function, in the introduction of fluids into the ports of the microfluidic devices. Specifically, wider openings facilitate introduction of fluids into the reservoir.

Detailed Description Paragraph Right (34):
Also as shown, the lower planar surface 204 of the cover layer 200, has fabricated thereon, a series of raised ridges 212, which function as alignment structures to ensure the body structure of the microfluidic device 100 (from FIG. 1), is properly aligned with the cover layer during the bonding or mating process. Although illustrated as ridges, it will be understood that a number of different alignment structures may be provided upon the lower planar surface for aligning the body structure of the device with the cover layer. For example, a recessed region, which is configured to fit the body structure may be used, whereby placement of the body structure into the recessed region positions the body structure to be appropriately aligned with the apertures in the cover layer. Alternatively, alignment pins may be provided extending from the lower surface, against which the body structure may rest, when appropriately aligned with the cover layer.

Detailed Description Paragraph Right (36):
As shown, the cover layer 200 includes side-walls 216, which extend from the lower planar surface 204, effectively creating a hollow-backed structure. This hollow-backed structure permits the mounting of a body structure of a microfluidic device to the lower surface of the cover layer without altering the overall profile of the cover layer, e.g., permitting the combined device-cover layer to be laid flat upon a surface or stacked with other like devices, as well as providing benefits in manufacturing, e.g., curing/hardening of molded parts, etc.

Detailed Description Paragraph Right (38):
As shown in FIG. 2A, the cover layer also includes convenience features. For example, textured regions 222 are provided on side-walls 216, to provide gripping surfaces for manual handling of the cover layer and assembled device. Also provided is registry port 224 disposed through the cover layer. Different numbers, sizes and/or shapes of registry ports are optionally provided in the cover layer to register the type of microfluidic device that has been inserted in a controller/detector instrument. This ensures that the proper interface is used, and/or the proper control program is being run.

Detailed Description Paragraph Right (39):
FIG. 3A illustrates the fully assembled microfluidic device 300 including the body structure 100 mated with the lower surface of the cover layer 200, and bonded using, e.g., an adhesive, as described above. The dimensions of planar devices, e.g., as shown in FIG. 3A, can vary substantially depending upon the application for which the device is to be used. Typically, however, the fully assembled devices have a rectangular shape and range from about 5 mm to about 200 mm on a side, and preferably are in the range of from about 10 mm to about 100 mm, and still more preferably, in the range of from about 20 mm to about 70 mm, e.g., about 50 mm on a side. For example, a square device approximately 50 mm on a side is shown. Such devices provide ease of handling as well as ready access to equipment already sized for handling substrates of this size, i.e., photographic slides.

Detailed Description Paragraph Right (41):
Although illustrated as a planar cover layer attached to a planar body structure, it will be appreciated that an appropriate cover layer is optionally joined to a non-planar microfluidic system, e.g., a tubular capillary or the like. In such cases, apertures in the cover layer are again fabricated to align with the ports, e.g., inlets and outlets of the capillary channel.

Detailed Description Paragraph Right (42):
In addition to the above-noted advantages, e.g., isolation of reservoirs, increased reservoir volume, etc., the cover layers described for use in conjunction with the present invention also optionally include other useful features. For example, the shape of the aperture in the cover layer is optionally configured to receive a complementary structure on a filling apparatus, e.g., syringe or pump. Specifically, in some cases it is desirable to use a positive pressure source to assist in filling the channel networks of a microfluidic device with fluid. This is typically useful where the filling solution, e.g., running buffer, separation matrix, etc., is slower at wicking

into the channel network via capillary action, due to viscosity effects. In operation, the running buffer, separation matrix, etc. is placed into one reservoir of the microfluidic device. A positive pressure is then applied to that reservoir thereby forcing the fluid throughout the channel network.

Detailed Description Paragraph Right (45):
Additional functions are also optionally performed by the cover layer. For example, in some cases, it may be desirable to perform a separation function, e.g., a filtration, cell separation, molecular weight separation, affinity, charge-based or hydrophobic interaction type separations, on a sample that is to be introduced into the microfluidic device. Accordingly, an appropriate filtration or separation medium or membrane is optionally provided within or across the aperture on the cover layer. When the cover layer is mated to the body structure of the device, introduction of a sample into the body structure requires passage through the filter or membrane, and separation of particulate components, high molecular weight materials, and the like.

Detailed Description Paragraph Right (46):
In further aspects, the cover layer performs a fluid handling and direction function, e.g, a manifolding function, where an aperture in the cover layer communicates with more than one reservoir on the body structure of the device, e.g., 2, 3, 4, 5, 10 or even 20 different reservoirs. Such a system is particularly useful where a single sample is to be subject to multiple different analyses within body structure of the microfluidic device, e.g., in diagnostic applications where a single patient sample may be subject to multiple diagnostic tests. A variety of other modifications will be apparent to one of ordinary skill in the art, and are generally encompassed by the present invention, as set forth in the appended claims.

Detailed Description Paragraph Right (47):
Alternatively, the cover layer may include other components useful in the operation of the microfluidic device and system, including e.g., integrated optical elements, e.g., lenses, gratings, coatings, polished detection windows, etc., as described in commonly owned U.S. patent application Ser. No. 09/030,535 now U.S. Pat. No. 6,100,541 , entitled "Microfluidic Devices and Systems Incorporating Integrated Optical Elements," filed of even date which is incorporated herein by reference, in its entirety for all purposes. Such elements supplement or replace optical elements from an external detection system.

Detailed Description Paragraph Right (48):
As alluded to above, the microfluidic devices described herein, are generally operated in conjunction with a controller instrument. Typical controller instruments include material transport systems, for affecting material, e.g., fluid, movement within and among the channels and chambers of a microfluidic device. For example, in the case of microfluidic systems employing pressure based fluid flow or that incorporate pressure actuated micropumps and valves, the controller instrument typically includes pressure sources as well as appropriate manifolds for delivering the appropriate pressures to complementary ports on the microfluidic device. The instrument then applies pressure/vacuum to activate the pumps and valves, or directly to fluids, to move those fluids through the channels of the device in a controlled fashion. In the case of microfluidic systems employing electrokinetic material transport systems, the controller typically includes an electrical power supply that is capable of delivering voltage gradients across the length of channels within the microfluidic device, as described above, when the device is mounted in the controller. Examples of particularly preferred power supplies are described in, e.g., Published International Application No. WO 98/00707, which is incorporated herein by reference in its entirety for all purposes.

Detailed Description Paragraph Right (49):
As such, the controller typically includes an appropriate interface for delivering the voltage gradients to the channels of the device. Such interfaces are generally described in detail in commonly owned U.S. patent appplication Ser. No. 08/919,707, filed Oct. 9, 1997 now U.S. Pat. No. 5,989,402, and incorporated herein by reference for all purposes. In brief, such interfaces typically include a number of electrodes, operably coupled to electrical leads from the power supply. The controller also typically includes a nesting region, e.g., a well or platform, upon which the microfluidic device is mounted. The electrodes are positioned so as to be placed into electrical contact with the channels of the device. In preferred aspects, this is accomplished by providing a "clam shell" lid hinged to the nesting region so as to close over the top of the device. The device, e.g., as shown in FIGS. 1-3, is mounted on the nesting region with the reservoirs facing upward. The electrodes protruding from

the lower surface of the clam-shell lid then insert into the reservoirs on the upper surface of the microfluidic device when the clam-shell lid is closed, so as to be placed into electrical contact with fluids in those reservoirs.

Detailed Description Paragraph Right (50):
Environmental control elements are optionally included in the controller instrument, e.g., for maintaining the environmental conditions to which the microfluidic device is exposed, at optimal levels. For example, the controller optionally includes a thermal control element, e.g., a heating block, peltier device, etc.

Detailed Description Paragraph Right (51):
In addition to including control elements, in preferred aspects, the controller instrument also includes a detection system for detecting the results of an operation performed in the microfluidic device. As such, the instrument is also referred to as a controller/detector instrument.

Detailed Description Paragraph Right (52):
Examples of particularly preferred detection systems include fluorescent detection systems. Typically, these detection systems include a light source, such as a laser, laser diode, LED or high intensity lamp, within the controller/detector instrument. The detection system also typically includes appropriate optics, e.g., lenses, beam splitters, filters, dichroics, and the like, for directing the light source at the detection window of a microfluidic device mounted on the controller/detector. The optics also gather emitted fluorescence emanating from the channel(s) of the device, separate out reflected excitation light, and detect the emitted fluorescence, e.g., using a photodiode or photomultiplier tube (PMT). Other optical detection systems are optionally included within the controller/detector instrument, e.g., absorbance or colorimetric detection systems, and the like. Both fluorescence based and absorbance based detection systems are well known in the art.

Current US Original Classification (1):
422/102

Current US Cross Reference Classification (1):
422/100

Current US Cross Reference Classification (2):
422/103

Current US Cross Reference Classification (3):
422/104

Current US Cross Reference Classification (4):
422/68.1

Current US Cross Reference Classification (5):
422/99

Current US Cross Reference Classification (6):
436/174

Current US Cross Reference Classification (7):
436/179

Current US Cross Reference Classification (8):
436/180

Other Reference Publication (3):
Jacobson, S.C. et al., "Fused Quartz Substrates for Microchip Electrophoresis," Anal. Chem. 67:2059-2063 (1995).

CLAIMS:

1. A microfluidic device, comprising:

a body structure comprising at least a first microscale channel network disposed therein, the body structure having a plurality of ports disposed in the body structure, each port being in fluid communication with one or more channels in the first channel network; and

a cover layer comprising a plurality of apertures disposed through the cover layer, the cover layer being mated with the body structure whereby each of the apertures is aligned with at least one of the plurality of ports.

2. The microfluidic device of claim 1, wherein each of the body structure and the cover layer separately comprises at least a first surface, the plurality of ports being disposed in the first surface of the body structure, and the plurality of apertures being disposed in the first surface of the cover layer, the first surface of the cover layer being mated to the first surface of the body structure such that the apertures align with and are in fluid communication with the ports.

3. The microfluidic device of claim 1, wherein the first surface of the body structure and the first surface of the cover layer are planar.

4. The microfluidic device of claim 1, wherein the cover layer further comprises:

a second surface opposite the first surface, the apertures extending from the first surface to the second surface; and

a plurality of raised annular ridges disposed on the second surface, the ridges surrounding each of the apertures.

5. The microfluidic device of claim 4, wherein the ridges are raised at least 0.5 mm relative to the second surface of the cover layer.

6. The microfluidic device of claim 4, wherein the ridges are raised at least 1 mm relative to the second surface of the cover layer.

7. The microfluidic device of claim 4, Wherein the ridges are raised at least 2 mm relative to the second surface of the cover layer.

8. The microfluidic device of claim 1, wherein the apertures are at least 1 mm deep.

9. The microfluidic device of claim 1, wherein the apertures are at least 2 mm deep.

10. The microfluidic device of claim 1, wherein the apertures are at least 5 mm deep.

11. The microfluidic device of claim 4, wherein the second surface of the cover layer comprises a hydrophobic polymer.

12. The microfluidic device of claim 11, wherein the hydrophobic polymer comprises polytetrafluoroethylene.

13. The microfluidic device of claim 1, wherein alignment of the apertures with the wells results in a plurality of reservoirs, each of the reservoirs having a volume of at least 10 .mu.l.

14. The microfluidic device of claim 1, wherein alignment of the apertures with the wells results in a plurality of reservoirs, each of the reservoirs having a volume of at least 20 .mu.l.

15. The microfluidic device of claim 1, wherein alignment of the apertures with the wells results in a plurality of reservoirs, each of the reservoirs having a volume of at least 50 .mu.l.

16. The microfluidic device of claim 1, wherein alignment of the apertures with the wells results in a plurality of reservoirs, each of the reservoirs having a volume of at least 100 .mu.l.

17. The microfluidic device of claim 1, wherein alignment of the apertures with the wells results in a plurality of reservoirs, each of the reservoirs having a volume of between about 5 and about 200 .mu.l.

18. The microfluidic device of claim 1, wherein alignment of the apertures with the wells results in a plurality of reservoirs, each of the reservoirs having a volume of between about 10 and about 100 .mu.l.

19. The microfluidic device of claim 1, wherein the cover layer is bonded to the first

surface of the body structure with an adhesive.

20. The microfluidic device of claim 19, wherein the adhesive is a UV curable adhesive.

21. The microfluidic device of claim 1, wherein the cover layer is clamped to the first surface of the body structure.

22. The microfluidic device of claim 21, further comprising a gasket disposed between the cover layer and the first surface of the body structure.

23. The microfluidic device of claim 1, wherein the cover layer further comprises at least a first alignment structure for aligning the body structure on the first surface of the cover layer.

24. The microfluidic device of claim 23, wherein the first alignment structure comprises one or more raised ridges disposed around a perimeter of the plurality of apertures.

25. The microfluidic device of claim 23, wherein the first alignment structure comprises a recessed portion of the first surface of the cover layer.

26. The microfluidic device of claim 23, wherein the first alignment structure comprises a plurality of alignment pins extending from the first surface of the cover layer.

27. The microfluidic device of claim 23, wherein the cover layer comprises at least a second alignment structure complementary to an alignment structure on a controller/detector apparatus, to align the microfluidic device in the controller/detector apparatus.

28. The microfluidic device of claim 27, wherein the second alignment structure comprises one or more alignment holes, and the complementary alignment structure comprises one or more alignment pins.

29. The microfluidic device of claim 27, wherein the second alignment structure comprises an irregular edge of the cover layer.

30. The microfluidic device of claim 27, wherein the irregular edge comprises a beveled comer of the cover layer.

31. The microfluidic device of claim 1, wherein the apertures are disposed in the cover layer in a grid pattern on approximately 9 mm centers.

32. The microfluidic device of claim 1, wherein the apertures are disposed in the cover layer in a grid pattern on approximately 4.5 mm centers.

33. The microfluidic device of claim 1, wherein the cover layer is fabricated from a polymeric material.

34. The microfluidic device of claim 33, wherein the cover layer is an injection molded polymeric part.

35. The microfluidic device of claim 33, wherein the cover layer is a cast polymer part.

36. The microfluidic device of claim 1, wherein the body structure comprises:

a first planar substrate having at least a first surface, at least a first groove fabricated into the first surface of the first substrate; and

a second planar substrate overlaying and bonded to the first planar substrate, sealing the groove to form the at least first channel network, the second planar substrate including a plurality of ports disposed therethrough, the ports communicating with the at least first channel network.

37. The microfluidic device of claim 36, wherein the first and second planar substrates comprise silica based substrates.

38. The microfluidic device of claim 37, wherein the silica based substrate is glass.

39. The microfluidic device of claim 36, wherein the first and second substrates comprise polymeric substrates.

40. The microfluidic device of claim 39, wherein the polymeric substrate is selected from polymethylmethacrylate (PMMA), polycarbonate, polytetrafluoroethylene, polyvinylchloride (PVC), polydimethylsiloxane (PDMS), polysulfone, polystyrene, polymethylpentene, polypropylene, polyethylene, polyvinylidine fluoride and ABS.

41. The microfluidic device of claim 1, wherein the microfluidic device/cover layer comprises a rectangle measuring approximately 50 mm on at least one edge.

42. microfluidic device of claim 41, wherein the microfluidic device comprises a square shape measuring approximately 50 mm.times.50 mm.

43. A microfluidic device, comprising:

a body structure comprising at least a first channel network disposed therein, and a plurality of reservoirs disposed at and in fluid communication with different points of the channel network;

a cover layer comprising a plurality of apertures disposed therethrough each aperture forming at least a portion of a separate one of the plurality of reservoirs, wherein the cover layer further comprises a plurality of raised ridges extending from and surrounding an outer edge of each of the apertures.

44. A microfluidic system, comprising:

a microfluidic device of claim 1; and

a controller/detector apparatus configured to receive the microfluidic device, the controller/detector apparatus comprising an optical detection system and a material transport system, the detection system and transport system being operably interfaced with the microfluidic device.

32. Document ID: US 6248229 B1

L23: Entry 32 of 94 File: USPT Jun 19, 2001

US-PAT-NO: 6248229
DOCUMENT-IDENTIFIER: US 6248229 B1

TITLE: Detection of analytes using reorganization energy

L23: Entry 32 of 94 File: USPT Jun 19, 2001

US-PAT-NO: 6248229
DOCUMENT-IDENTIFIER: US 6248229 B1

TITLE: Detection of analytes using reorganization energy

DATE-ISSUED: June 19, 2001

US-CL-CURRENT: 205/777.5; 205/775, 205/778, 205/779, 205/793.5, 422/68.1, 422/82.01, 422/82.02, 435/4, 435/5, 435/6, 435/7.2, 435/7.3, 435/7.4, 435/7.6, 435/7.71, 435/7.72, 435/7.8, 435/7.9, 435/7.91, 435/7.92, 435/7.93

APPL-NO: 9/ 417988
DATE FILED: October 13, 1999

PARENT-CASE:

This is a continuation of application Ser. No. 09/096,504 filed Jun. 12, 1998, now U.S. Pat. No. 6,013,170 which is the continuation of 08/873,977 filed Jun. 12, 1997 now U.S. Pat. No. 6,013,459.

L23: Entry 32 of 94 File: USPT Jun 19, 2001

DOCUMENT-IDENTIFIER: US 6248229 B1
TITLE: Detection of analytes using reorganization energy

Current US Cross Reference Classification (5):
422/68.1

Current US Cross Reference Classification (6):
422/82.01

Current US Cross Reference Classification (7):
422/82.02

Current US Cross Reference Classification (8):
435/4

Current US Cross Reference Classification (9):
435/5

Current US Cross Reference Classification (10):
435/6

Current US Cross Reference Classification (11):
435/7.2

Current US Cross Reference Classification (12):
435/7.3

Current US Cross Reference Classification (13):
435/7.4

Current US Cross Reference Classification (14):
435/7.6

Current US Cross Reference Classification (15):
435/7.71

Current US Cross Reference Classification (16):
435/7.72

Current US Cross Reference Classification (17):
435/7.8

Current US Cross Reference Classification (18):
435/7.9

Current US Cross Reference Classification (19):
435/7.91

Current US Cross Reference Classification (20):
435/7.92

Current US Cross Reference Classification (21):
435/7.93

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):

Chrisey, et al., Covalent attachment of synthetic DNA to self-assembled monolayer fi Research, 24(15):3031-3039 (1996).

Other Reference Publication (68):
Palecek, From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Elect Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (72):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-F undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (77):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Protein Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (84):
Tour, et al., Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, an Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surface Soc., 117:9529-9534 (1995).

Other Reference Publication (88):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electr Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

CLAIMS:

7. A composition according to claim 1 wherein said electrode further comprises a self-assembled monolayer.

18. An apparatus according to claim 11 wherein said first electrode further comprises a self-assembled monolayer.

33. Document ID: US 6242264 B1

L23: Entry 33 of 94 File: USPT Jun 5, 2001

US-PAT-NO: 6242264
DOCUMENT-IDENTIFIER: US 6242264 B1

TITLE: Self-assembled metal colloid monolayers having size and density gradients

L23: Entry 33 of 94 File: USPT Jun 5, 2001

US-PAT-NO: 6242264
DOCUMENT-IDENTIFIER: US 6242264 B1

TITLE: Self-assembled metal colloid monolayers having size and density gradients

DATE-ISSUED: June 5, 2001

US-CL-CURRENT: 436/171; 422/68.1, 422/82.01, 422/82.02, 422/82.03, 422/82.05, 422/82.08, 422/82.09, 436/164, 436/501, 436/514, 436/525, 436/86

APPL-NO: 9/ 254142
DATE FILED: January 12, 2000

PARENT-CASE:

This is the National Stage of International Application No. PCT/US97/15581, filed Sep. 4, 1997; which is a continuation-in-part of application Ser. No. 08/769,970, filed Dec. 19, 1996, now abandoned and which claims the benefit of U.S. Provisional Application No. 60/025,064, filed Sep. 4, 1996.

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/US97/15581	September 4, 1997	WO98/10289	Mar 12, 1998	Jan 12, 2000	Jan 12, 2000

L23: Entry 33 of 94 File: USPT Jun 5, 2001

DOCUMENT-IDENTIFIER: US 6242264 B1
TITLE: Self-assembled metal colloid monolayers having size and density gradients

Detailed Description Paragraph Right (29):
Materials. The following materials were obtained from Aldrich: HAuCl.sub.4.3H.sub.2 O, AgNO.sub.3, trisodium citrate dihydrate, trans-1,2 bis(4-pyridyl)ethylene (BPE), and trimethoxy-propylsilane. The following organosilanes were obtained from Huls America, Inc., and used as received: (3-aminopropyl)trimethoxysilane (APTMS), (3-cyanopropyldimethyl)methoxysilane (CPDMMS), (3-mercaptopropylmethyl)dimethoxysilane (MPMDMS), and 3-cyanopropyltriethoxysilane (CPTES). Concentrated HCl, HNO.sub.3, and H.sub.2 SO.sub.4 were purchased from J. T. Baker Inc., and 30% H.sub.2 O.sub.2 was obtained from VWR. CH.sub.3 OH (spectrophotometric grade) was obtained from EM Science; all H.sub.2 O was 18 MW, distilled through a Barnstead Nanopure water purification system. Streptavidin, bovine serum albumin (BSA), and 3-(N-maleimidopropionyl)biocytin (MP-biocytin) were purchased from Sigma. BPE was recrystallized several times from a mixture of H.sub.2 O and CH.sub.3 OH; the other materials were used as received. Substrates were obtained as follows: glass and quartz microscope slides from Fisher Scientific and Technical Glass Products, respectively; SiO.sub.x -coated TEM grids from Ted Pella, Inc.; and self-assembled monolayers (SAMs) of HS(CH.sub.2).sub.18 CO.sub.2 H on Au foil from literature procedures [Bain, C. D.; Troughton, E. B.; Tao, Y.-T.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. J. Am. Chem. Soc. 1989, 111, 321-35].

Detailed Description Paragraph Right (69):
The Au and Ag colloid-based surfaces have many of the best attributes of previously described SERS substrates (uniform particle size, electrochemical addressability, and large enhancement factors), and a combination of other features few surfaces can match (ease of characterization, no geometric constraints, low cost, and very high intra- and inter-sample reproducibility). When the substrate is optically transparent in the visible, uv-vis can be used to assess particle coverage and spacing. These substrates are strongly active for SERS using 647.1 nm excitation, as are those prepared on glass and quartz slides. These advantages, coupled with the ability to vary particle size, spacing, and the nature of the monolayer support suggest a rich use for these materials in fundamental and applied studies. For example, no theoretical model correlating SERS activity with particle size or spacing has ever been quantitatively tested; metal colloid monolayers should allow such experiments to be carried out. The flexibility and control available through this method are noteworthy. Particle size, particle-polymer interactions, and the physical and chemical properties of the underlying substrate can all be manipulated to control the nanoscale architecture produced. The solution-based assembly protocol makes substrate fabrication routine; it also removes virtually all constraints on substrate size/shape. Therefore, Au colloid monolayers can be prepared on substrates that allow facile characterization, including macroscopic glass/quartz slides and TEM grids. Most importantly, SERS can now be considered for applications in which preparation of multiple high-quality substrates was previously viewed as an insurmountable barrier.

Detailed Description Paragraph Right (92):
The most likely interferences in SERS are adsorption of inorganic anions (HO.sup.31, HCOO.sup.31, etc.) Their influence can be minimized by acidifcation; at pH 5, [HO.sup.-]=10.sup.-9. Thus a simple route to identify (and eliminate) undesired adsorbates is to acquire Raman spectra at several pH's. Halide anions are bound more tightly, but each have only one band in the Raman spectrum, so that their net effect is essentially limited to a reduction of available OPP binding sites. If this leads to significant problems, it can be overcome by introducing an element of molecular selectivity at the Au/Ag interface. The introduction of organothiol self-assembled monolayers (SAMs) onto SERS-active surfaces increases selectivity for the desired analytes, and that partition

from solution into the SAM film can be quantitated. A similar strategy can be adopted with regard to the inventive method using HSCH.sub.2 CH.sub.2 OH or HSCH.sub.2 CH.sub.2 NH.sub.3.sup.+. Monolayers of the first molecule should preferentially hydrogen bond with the P=S or P=O functional group relative to H.sub.2 O, HO.sup.-, or halide. Note that direct analyte adsorption is not necessary for SERS: enhancement by the so-called electromagnetic effect--which accounts for 10.sup.4 of the 10.sup.6 overall enhancement--is still quite substantial 10 .ANG. from the surface.

Current US Original Classification (1):
436/171

Current US Cross Reference Classification (1):
422/68.1

Current US Cross Reference Classification (2):
422/82.01

Current US Cross Reference Classification (3):
422/82.02

Current US Cross Reference Classification (4):
422/82.03

Current US Cross Reference Classification (5):
422/82.05

Current US Cross Reference Classification (6):
422/82.08

Current US Cross Reference Classification (7):
422/82.09

Current US Cross Reference Classification (8):
436/164

Current US Cross Reference Classification (9):
436/501

Current US Cross Reference Classification (10):
436/514

Current US Cross Reference Classification (11):
436/525

Current US Cross Reference Classification (12):
436/86

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

34. Document ID: US 6238870 B1

L23: Entry 34 of 94 File: USPT May 29, 2001

US-PAT-NO: 6238870
DOCUMENT-IDENTIFIER: US 6238870 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 34 of 94 File: USPT May 29, 2001

US-PAT-NO: 6238870
DOCUMENT-IDENTIFIER: US 6238870 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: May 29, 2001

US-CL-CURRENT: 435/6; 536/23.1, 536/24.3

APPL-NO: 9/ 458187
DATE FILED: December 8, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This application is a continuing application of U.S. Ser. No. 09/306,749, filed May 7, 1999, which is a continuing application of 08/873,598, filed Jun. 12, 1997, U.S. Pat. No. 5,952,172, which is a continuing application of U.S. Ser. No. 08/660,534, filed Jun. 7, 1996, U.S. Pat. No. 5,770,369, which is a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995, U.S. Pat. No. 5,824,473, which is a continuing application of U.S. Ser. No. 08/166,036, filed Dec. 10, 1993, U.S. Pat. No. 5,591,578.

L23: Entry 34 of 94 File: USPT May 29, 2001

DOCUMENT-IDENTIFIER: US 6238870 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

Other Reference Publication (102):
Fotin, A. et al., "Potential Thermodynamic Analysis of Duplexes on Oligodeoxyribonucleotide Microchips," Nucleic Acids Research, 216(6):1515-1521 (1998).

Other Reference Publication (103):
Guschin, D. et al., "Manual Manufacturing of Oligonucleotide, DNA, and Protein Microchips," Analytical Biochemistry, 250:203-211 (1997).

Other Reference Publication (104):
Dubiley, S. et al., "Fractionation, phosphorylation and Ligation on Oligonucleotide Microchips to Enhance Sequencing by Hybridization," Nucleic Acids Research, 25(12):2259-2265 (1997).

Other Reference Publication (105):
Guschin, D. et al., "Oligonucleotide Microchips as Genosensors for Determinative and Environmental Studies in Microbiology," 63(6):2397-2402 (1997).

Other Reference Publication (111):
Parinov, S., "DNA Sequencing by Hybridization to Microchip octa- and Decanucleotides Extended by Stacked Pentanucleotides," Nucleic Acids Research, 24(15):2998-3004 (1996).

Other Reference Publication (112):
Yershov, G. et al., "DNA Analysis and Diagnostics on Oligonucleotide Microchips," Proc. Natl. Acad. Sci. USA, 93:4913-4918 (1996).

Other Reference Publication (115):
Proudnikov, D. "Immobilization of DNA in Polyacrylamide Gel for the manufacture of DNA and DNA-Oligonucleotide Microchips," Analytical Chemistry, 259:34-41 (1998).

35. Document ID: US 6232062 B1

L23: Entry 35 of 94 File: USPT May 15, 2001

US-PAT-NO: 6232062
DOCUMENT-IDENTIFIER: US 6232062 B1

TITLE: AC methods for the detection of nucleic acids

L23: Entry 35 of 94 File: USPT May 15, 2001

US-PAT-NO: 6232062
DOCUMENT-IDENTIFIER: US 6232062 B1

TITLE: AC methods for the detection of nucleic acids

DATE-ISSUED: May 15, 2001

US-CL-CURRENT: 435/6; 536/23.1, 536/24.3

APPL-NO: 8/ 911589
DATE FILED: August 14, 1997

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This is a continuing application of U.S. Ser. No. 08/873,597, filed Jun. 12, 1997, which claims priority to U.S. provisional application Ser. No. 60/040,155, filed Mar. 7, 1997.

L23: Entry 35 of 94 File: USPT May 15, 2001

DOCUMENT-IDENTIFIER: US 6232062 B1
TITLE: AC methods for the detection of nucleic acids

Current US Original Classification (1):
435/6

Other Reference Publication (16):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Aklanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (17):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (70):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (75):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (80):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (87):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (91):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

36. Document ID: US 6225109 B1

L23: Entry 36 of 94 File: USPT May 1, 2001

US-PAT-NO: 6225109
DOCUMENT-IDENTIFIER: US 6225109 B1

TITLE: Genetic analysis device

L23: Entry 36 of 94 File: USPT May 1, 2001

US-PAT-NO: 6225109
DOCUMENT-IDENTIFIER: US 6225109 B1

TITLE: Genetic analysis device

DATE-ISSUED: May 1, 2001

US-CL-CURRENT: 435/288.5; 422/50, 422/58, 422/68.1, 435/287.2, 435/288.3, 435/6

APPL-NO: 9/ 321170
DATE FILED: May 27, 1999

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
This application is related to the subject matter of simultaneously filed U.S. patent application Ser. No. 09/321,410, entitled "Multiple Fluid Sample Processor and System"

(Docket No. ORCH 0116 PUS). The disclosure of which is hereby incorporated by reference herein.

L23: Entry 36 of 94 File: USPT May 1, 2001

DOCUMENT-IDENTIFIER: US 6225109 B1
TITLE: Genetic analysis device

Detailed Description Paragraph Right (7):
The middle layer 15 is preferably fabricated by a molding process and is formed with a plurality of inlet ports or openings 23, outlet ports or openings 24, micro channels 25 and 26, and recessed reaction or assay areas 27. A wide variety of widths, lengths, and depths of ports, channels and reaction areas can be utilized with the present invention. Preferably, eight inlet ports, reaction areas and outlet ports are provided in each assay device 10. This allows a group of twelve devices to be positioned in a support base, as discussed below, and be arranged in a microtiter format. The "pitch" or distance between the centers of the ports 23 is 9 mm. Of course, it is to be understood that the present invention is not limited to such number of ports and pitch dimension, any number and dimension can be utilized as desired.

Detailed Description Paragraph Right (19):
When assembled, the middle layer 34 is in slight compression by the other members of the device. Also, a raised ridge or boss surrounds each inlet and outlet port. The bosses press into the middle layer providing individual seals to each port.

Detailed Description Paragraph Right (43):
The cover member 152 has an opening or port 170 which aligns with opening or port 172 in the elastomer member 154. DNA, reagents, wash materials and the like are introduced into the assay device 150 through ports 170 and 172. Small micro channel 174 formed in the bottom of elastomer member 154 conveys the materials to reaction recess 176 which is positioned over the spots of oligo arrays 166. Window 180 in cover member 152 allows visual inspection of the passage of the materials through recess 176 during the assay process.

Detailed Description Paragraph Right (44):
An absorbent member 156, such as a small pad or sponge, is positioned in the cavity 178. The absorbent member 156 soaks up the excess DNA, reagents and wash materials which are introduced into the device and passed over the arrays 166. Microchannel 179 conveys these materials from the reaction recess 176 to the cavity 178. The absorbent material takes up only excess fluid exiting the array cavity or recess, and is prevented from completely draining the chamber by means of the separating channel or void. The single sample device is disposable. Once the assay is completed, the housing (cover member) 152, elastomer member 154 and absorbent member 156 can be discarded.

Detailed Description Paragraph Right (50):
The devices 200 are preferably provided with a construction and assembly similar to devices 10, 28, and/or 70 set forth and described above. In this regard, one or two glass slide members are provided in each device 200, together with a conformable molded elastomer middle layer and a plastic housing. Microchannels and reaction recesses are also provided in the middle layer in communication with the ports 212.

Current US Original Classification (1):
435/288.5

Current US Cross Reference Classification (1):
422/50

Current US Cross Reference Classification (2):
422/58

Current US Cross Reference Classification (3):
422/68.1

Current US Cross Reference Classification (4):
435/287.2

Current US Cross Reference Classification (5):

435/288.3

Current US Cross Reference Classification (6):
435/6

37. Document ID: US 6221583 B1

L23: Entry 37 of 94 File: USPT Apr 24, 2001

US-PAT-NO: 6221583
DOCUMENT-IDENTIFIER: US 6221583 B1

TITLE: Methods of detecting nucleic acids using electrodes

L23: Entry 37 of 94 File: USPT Apr 24, 2001

US-PAT-NO: 6221583
DOCUMENT-IDENTIFIER: US 6221583 B1

TITLE: Methods of detecting nucleic acids using electrodes

DATE-ISSUED: April 24, 2001

US-CL-CURRENT: 435/6; 422/50, 422/68.1, 436/501

APPL-NO: 8/ 899510
DATE FILED: July 24, 1997

PARENT-CASE:

This is a division of application Ser. No. 08/743,798 filed Nov. 5, 1996.

L23: Entry 37 of 94 File: USPT Apr 24, 2001

DOCUMENT-IDENTIFIER: US 6221583 B1
TITLE: Methods of detecting nucleic acids using electrodes

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
422/50

Current US Cross Reference Classification (2):
422/68.1

Current US Cross Reference Classification (3):
436/501

Other Reference Publication (14):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (15):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (68):

Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (73):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (78):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (85):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thios, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (89):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

38. Document ID: US 6210910 B1

L23: Entry 38 of 94 File: USPT Apr 3, 2001

US-PAT-NO: 6210910
DOCUMENT-IDENTIFIER: US 6210910 B1

TITLE: Optical fiber biosensor array comprising cell populations confined to microcavities

L23: Entry 38 of 94 File: USPT Apr 3, 2001

US-PAT-NO: 6210910
DOCUMENT-IDENTIFIER: US 6210910 B1

TITLE: Optical fiber biosensor array comprising cell populations confined to microcavities

DATE-ISSUED: April 3, 2001

US-CL-CURRENT: 435/7.32; 385/115, 385/12, 385/123, 422/57, 422/58, 422/82.05, 422/82.08, 422/82.11, 435/287.1, 435/288.7 , 435/7.2, 435/7.21, 435/808, 436/164, 436/165, 436/172, 436/518, 436/524, 436/527, 436/535, 436/805

APPL-NO: 9/ 033462
DATE FILED: March 2, 1998

L23: Entry 38 of 94 File: USPT Apr 3, 2001

DOCUMENT-IDENTIFIER: US 6210910 B1
TITLE: Optical fiber biosensor array comprising cell populations confined to microcavities

Brief Summary Paragraph Right (2):
It is generally recognized that important technical advances in chemistry, biology and medicine benefit from the ability to perform microanalysis of samples in minute quantities. However, making analytical measurements on minute quantities has long been

a challenge due to difficulties encountered with small volume sample handling, isolation of analytes, and micro-analysis of single-cell physiology.

Brief Summary Paragraph Right (4):
Clark, et al. [Anal. Chem. 69(2):259(1997)] has disclosed a method for fabricating picoliter microvials for electrochemical microanalysis using conventional photolithographic masking and photoresist techniques to transfer mold polystyrene microvials on silicon wafer templates. These microvials typically exhibit non-uniformity in size and shape due to the difficulty in controlling the resist etching of the molding surface and the transfer molding process.

Brief Summary Paragraph Right (14):
Regnier, et al., [Trends in Anal. Chem. 14(4):177(1995)] discloses an invasive, electrophoretically mediated, microanalysis method for single cell analysis. The method utilizes a tapered microinjector at the injection end of a capillary electrophoresis column to pierce an individual cell membrane and withdraw a sample of cytoplasm. The method measures cell contents, one cell at a time. The method is generally limited to the detection of easily oxidized species.

Current US Original Classification (1):
435/7.32

Current US Cross Reference Classification (4):
422/57

Current US Cross Reference Classification (5):
422/58

Current US Cross Reference Classification (6):
422/82.05

Current US Cross Reference Classification (7):
422/82.08

Current US Cross Reference Classification (8):
422/82.11

Current US Cross Reference Classification (9):
435/287.1

Current US Cross Reference Classification (10):
435/288.7

Current US Cross Reference Classification (11):
435/7.2

Current US Cross Reference Classification (12):
435/7.21

Current US Cross Reference Classification (13):
435/808

Current US Cross Reference Classification (14):
436/164

Current US Cross Reference Classification (15):
436/165

Current US Cross Reference Classification (16):
436/172

Current US Cross Reference Classification (17):
436/518

Current US Cross Reference Classification (18):
436/524

Current US Cross Reference Classification (19):
436/527

Current US Cross Reference Classification (20):
436/535

Current US Cross Reference Classification (21):
436/805

Other Reference Publication (8):
M. Mrksich, et al., "Controlling Cell Attachment of Contored Surfaces with Self-assembled Monolayers of Alkanethiolates on Gold", Proc.Natl.Acad.Sci. USA, v. 93., pp. 10775-10778, Oct. 1996.

Other Reference Publication (37):
F.E. Regnier, et al., "Electrophoretically-mediated microanalysis", Trends in Analytical Chemistry, vol. 14, No. 4, pp. 177-181 (1995).

39. Document ID: US 6207369 B1

L23: Entry 39 of 94 File: USPT Mar 27, 2001

US-PAT-NO: 6207369
DOCUMENT-IDENTIFIER: US 6207369 B1

TITLE: Multi-array, multi-specific electrochemiluminescence testing

L23: Entry 39 of 94 File: USPT Mar 27, 2001

US-PAT-NO: 6207369
DOCUMENT-IDENTIFIER: US 6207369 B1

TITLE: Multi-array, multi-specific electrochemiluminescence testing

DATE-ISSUED: March 27, 2001

US-CL-CURRENT: 435/6; 204/400, 204/403.15, 422/50, 422/52, 422/55, 422/61, 422/82.05, 422/82.07, 422/82.08, 435/287.1, 435/287.2, 435/288.7, 435/808, 435/810, 435/968, 435/975, 436/164, 436/172, 436/518, 436/524, 436/534, 436/805

APPL-NO: 8/ 715163
DATE FILED: September 17, 1996

PARENT-CASE:

This application is a continuation-in-part of application Ser. No. 08/611,804 filed Mar. 6, 1996, now U.S. Pat. No. 6,066,448, which is a continuation-in-part of applications Ser. Nos. 08/402,076 filed Mar. 10, 1995, now abandoned and 08/402,277 filed Mar. 10, 1995, now abandoned each of which is incorporated by reference herein in its entirety.

L23: Entry 39 of 94 File: USPT Mar 27, 2001

DOCUMENT-IDENTIFIER: US 6207369 B1
TITLE: Multi-array, multi-specific electrochemiluminescence testing

Assignee Name (1):
Meso Scale Technologies, LLC

Assignee Name (Derived) (1):
Meso Scale Technologies, LLC

Brief Summary Paragraph Right (6):
The excitation of a TAG in an ECL reaction typically involves diffusion of the TAG molecule to the surface of an electrode. Other mechanisms for the excitation of a TAG molecule by an electrode include the use of electrochemical mediators in solution (Haapakka, 1982, Anal Chim. Acta, 141:263) and the capture of beads presenting TAG molecules on an electrode (PCT published applications WO 90/05301 and WO 92/14139). Alternatively, ECL has been observed from TAG that was adsorbed directly on the surface of working electrodes (U.S. Pat. No. 5,324,457), e.g., by non-specific adsorption (Xu et al., 1994, Langmuir, 10:2409-2414), by incorporation into L-B films (Zhang et al., 1988, J. Phys. Chem., 92:5566), by incorporation into self-assembled monolayers (Obeng et al., 1991, Langmuir, 7:195), and by incorporation into thick (micrometer) films (Rubenstein et al., 1981, J. Am. Chem. Soc., 102:6641). Similarly, Xu et al. (PCT published application WO 96/06946) have observed ECL from TAG molecules intercalated into DNA strands when such strands were adsorbed onto gold electrodes by interaction with aluminum centers immobilized on a self-assembled monolayer of alkanethiolates.

Drawing Description Paragraph Right (7):
FIG. 5B illustrates a top view of a microfluidics guide for delivering binding reagents and/or analytes to discrete binding domains. Each dot illustrates a cross section of a microfluidics guide (e.g., a capillary).

Drawing Description Paragraph Right (8):
FIG. 5C illustrates a side view of a microfluidics guide showing the approximation of registered or aligned microfluidic guides for delivering binding reagents and/or analytes to a multi array of patterned binding domains. Each microfluidic guide may deliver a different binding reagent to a discrete binding domain.

Drawing Description Paragraph Right (15):
FIG. 11 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self-assembled monolayers ("SAMs") is patterned on the metallic layer.

Drawing Description Paragraph Right (17):
FIG. 13 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self assembled monolayers or SAMs is patterned on the metallic layer and the growth of a conducting polymer and/or fiber from the ECL label so as to extend the potential field around the ECL label of the sample to increase the efficiency of the ECL reaction, is illustrated.

Drawing Description Paragraph Right (26):
FIG. 22A illustrates an array of microfluidics guides (2201) and a fibril mat (2200).

Detailed Description Paragraph Right (22):
To better understand the invention, a more detailed description of the preparation of binding domains on a support is provided. A patterned array of binding domains on a surface that are specific for a plurality of analytes is referred to herein as a patterned, multi-array multi-specific surface or PMAMS. PMAMS are prepared on a support, for example, by patterning of self-assembled monolayers ("SAMs") (Ferguson et al, 1993, Macromolecules 26(22):5870-5875; Prime et al., 1991, Science 252:1164-1167; Laibinis et al., 1989, Science 245:845-847; Kumar et al., 1984, Langmuir 10(5):1498-1511; Bain et al., 1989, Angew. Chem. 101:522-528). Surface patterning methods also include the use of physical etching (e.g., micromachining) (Abbott et al., 1992, Science 257:1380-1382; Abbott, 1994, Chem. Mater. 6(5):596-602), microlithography (Laibinis et al., 1989, Science 245:845-847), attachment of chemical groups to the surface through the use of photoactivatable chemistries (Sundberg et al., 1995, J. Am. Chem. Soc. 117(49):12050-12057), and micro-stamping techniques (Kumar et al., 1994, Langmuir 10(5):1498-1511; Kumar et al., 1993, Appl. Phys. Lett. 63(14):2002-2004). Other surface patterning methods include procedures for the spatially controlled dispensing of fluids or particles (e.g., micropen deposition (e.g., using a microfluidic guide to deliver onto a surface using X-Y translation)), microcapillary filling (Kim et al., 1995, Nature 376:581), Ink-Jet technology, or syringe dispensers. Combinations of these techniques may be used to provide complex surface patterns. In FIG. 5A, a support 600 is shown with shape independent binding domains that are represented, simply for illustration purposes, as geometric shapes 602 to indicate that different binding specificities may be present on a single support. Surface 604 between binding domains may be alternatively hydrophobic or hydrophilic to confine deposition of binding reagent to form binding domains. Binding domains and/or the surface(s)

between binding domains may be alternatively prone and resistant to nonspecific binding, and/or they may be prone and resistant to the attachment of binding reagents via covalent or non-covalent interactions. In the case where non-specific binding through hydrophobic interactions is not the desired method for attachment of binding chemistries to the surface, detergent may be added to prevent incidental non-specific binding from occurring.

Detailed Description Paragraph Right (33):
PMAMS can be generated from different types of surface binding groups. Self-assembling monolayers that can be used to form a monolayer on a surface to which they bind, include but are not limited to alkane thiols (which bind gold and other metals), alkyltrichlorosilane (e.g., which bind silicon/silicon dioxide), alkane carboxylic acids (e.g., which bind aluminum oxides) as well as combinations thereof. The monolayer may be formed first and then linking chemistry used to attach binding reagents. Derivatization after self-assembly produces a more perfect two-dimensional crystalline packing of the monolayer on a support surface with fewer pin holes or defects. The monolayer can be derivatized with the binding reagents before or after self-assembly. Regular defects in the monolayer may be desirable, and can be obtained by derivatization prior to self-assembly of the monolayer or the support surface. If the derivatized group (e.g., exposed binding group) on the binding reagent is sterically large, it may create a close-packed surface at the exposed end, but with regular gaps at the metal surface. This is useful for allowing charge to flow through these regular gaps to the ECL labeled moieties bound to the portion contacting the sample solution.

Detailed Description Paragraph Right (50):
Microfluidics guides may also be used to prepare the PMAMS binding domains on a support. A partial list of microfluidic guides includes hollow capillaries, capillaries made of and/or filled with a matrix (e.g., a porous or solvent swollen medium), solid supports which can support a thin film or drop of liquid. The capillary may be solid and reagents flow along the outside surface of the capillary, a reagent fluid reservoir may be exposed to a porous matrix tip which is brought into contact with a PMAMS surface. For example, the reagent reservoir may be continuously or periodically refilled so that a given porous matrix tip may reproducibly deposit reagents (e.g., alkane thiols to form monolayers and/or binding reagents etc.) a plurality of times. Additionally, varying the porosity of the tip can be utilized to control reagent flow to the surface. Different or identical binding reagents may be present in a plurality of capillaries and/or multiple distinct binding agents may be present in a given capillary. The capillaries are brought into contact with the PMAMS (e.g., patterned SAM) surface so that certain regions are exposed to the binding reagents so as to create discrete binding domains. Different binding reagents, each present in a different microfluidic guide are delivered concurrently from the fluidic guide array onto a metal surface, SAM, etc, as desired. Microfluidic guides can also be used to ink a microstamp with a desired molecule prior to application to the support surface. For example, individual microfluidic guides can be used to apply different binding reagents linked to a moiety that promotes adsorption to the surface of the support (e.g., a free thiol on a hydrocarbon linker, which promotes adsorption to gold), to form a PMAMS. Thus, for example, a microstamp inked via the use of microfluidic guides with antibodies of different specificities that have incorporated a linker with a free thiol, can be used to apply such antibodies in desired areas on a gold surface to form discrete binding domains of a PMAMS.

Detailed Description Paragraph Right (51):
Microfluidic guide also refers to microprinting devices which deliver microdrops of fluid by ejection of the drop through a small orifice (e.g., an Ink-Jet printer). The ejection drops in these devices may be caused by different mechanisms including heating, electrostatic charge, and/or pressure from a piezo device. Patterning of more than one liquid can be achieved through the use of multiple orifices and/or one orifice and appropriate valving.

Detailed Description Paragraph Right (52):
In one method for preparation of a PMAMS, microfluidic guides are used to deliver (preferably concurrently) directly onto discrete regions on a surface, drops containing the desired binding reagents, to form discrete binding domains. The binding reagents may contain a functional chemical group that forms a bond with a chemical group on the surface to which it is applied. In another variation, binding reagents in the drop are nonspecifically adsorbed or bound to the surface (e.g., dried on the surface).

Detailed Description Paragraph Right (54):
In a preferred technique, patterned hydrophilic/hydrophobic regions to prevent

spreading of applied fluids or gels can be used. Such a fluid or gel may contain binding reagents to be linked to a surface on a support to form a binding domain of the PMAMS. In this case, use of such a hydrophilic/hydrophobic border aids in confining the produced binding domain to a discrete area. Alternatively, the fluid contains reagents which can form a matrix on the surface and binding reagents are contained within a defined region when deposited on a surface. For example, hydrophilic/hydrophobic border aids may be utilized to confine the drop to a defined region. Additionally, either the hydrophilic or hydrophobic areas may present groups which can be incorporated (e.g., covalently or non-covalently bound) into the matrix, allowing for a more stable adhesion of the matrix to the substrate (Itaya and Bard, 1978, Anal. Chem. 50(11):1487-1489). In another technique, the fluid or gel that is applied is the sample containing the analyte of interest, and the sample is applied to a prepared PMAMS. In one preferred example, capillaries containing hydrophilic solutions can be used to deposit a solution onto discrete areas, creating hydrophilic domains surrounded by hydrophobic regions. Alternatively, hydrophobic binding domains surrounded by hydrophilic regions can be used with a hydrophobic fluid containing binding reagents or analyte(s)). Hydrophobic and hydrophilic are relative terms, with respect to each other and/or with respect to the sample to be applied, i.e., such that the spread or wetting of a fluid or gel sample applied to the binding domains is controlled. Further, controlled solution deposition from the microfluidics array may be accomplished using physical surface features (e.g., wells or channels on the surface). A microfluidics guide can be included in a cassette, or more preferably, used to apply specific reagents to a support prior to use.

Detailed Description Paragraph Right (56):
In particular, a PMAMS is generated by micro-contact printing, i.e., stamping. The monolayer so applied is composed of a surface-binding group, e.g., for a gold surface, a thiol group with an alkane (e.g., (CH.sub.2).sub.n)) spacer is preferred. A spacer group is linked (preferably covalently bound) to a linking group A. "A" can be, e.g., avidin, streptavidin or biotin or any other suitable binding reagent with an available complementary binding partner "B". The A:B linkage may be covalent or non-covalent and some linkage chemistries known to the art that can be used are disclosed by, e.g., Bard et al. (U.S. Pat. Nos. 5,221,605 and 5,310,687). "B" is further linked to a binding reagent such as an antibody, antigen, nucleic acid, pharmaceutical or other suitable substance for forming a binding domain that can bind to one or more analytes of interest in a sample to be tested. B may also be linked to an ECL TAG or label. Linking group B may be delivered to the SAM by means of a capillary or microfluidics guide array (FIGS. 5A-5C) able to place a plurality of "B" reagents with different binding surface specificities on the monolayer "A" linkage. A and B can also be linked before or prior to being attached to the monolayer. As discussed, in FIG. 5A, shape independent binding domains are represented, simply for illustration purposes as geometric shapes 602 to indicate that different binding specificities may be present on a single support 600. FIG. 5B provides a top view of a microfluidic guide (e.g., capillary) array 606. The dots 610 are the guides in cross section. FIG. 5C provides a side view of a microfluidic guide array 608. The lines emerging from the top and bottom are individual microfluidic guides 610. The geometric shapes 612 on the lower aspect represent specific binding domains formed upon delivery of binding reagent from each individual capillary.

Detailed Description Paragraph Right (65):
Binding domains located on a plurality of individual fibrils and/or aggregates of fibrils may be prepared on a support by means of one or more microfluidic guides (e.g., a capillary). Different or identical binding reagents may be present in or on a plurality of microfluidic guides and/or multiple distinct binding agents may be present in or on a given microfluidic guide. The capillaries may be brought into contact with the support (spotting) and/or may deliver the reagents while either the microfluidic guide and/or the surface is being scanned or translated relative to the other (i.e., a penlike method of writing). The microfluidic guide may deliver the binding reagents located on the fibrils to the support so that certain regions of the support are exposed to the fibril-binding reagent complex(es) so as to create a discrete binding domain(s). In a preferred aspect, different binding reagents, each present in a different microfluidic guide are delivered concurrently from the guide array onto the support. In one example, binding reagents and/or the fibrils on which they are localized are derivatized with a chemical functional group that forms a bond (e.g., covalent or non-covalent interaction) to the surface of the support. In some embodiments, the binding reagents and fibrils are non-specifically bound or adsorbed to the surface. In yet another aspect, the binding reagents localized on the fibrils may be delivered to depressions, pits and/or holes in the surface of the support. In another example, the binding reagents are delivered to a surface that is coated with a

material that has a stronger or weaker binding affinity for certain binding reagents or binding reagent/fibril ensembles and so creates domains of the reagents that are localized spatially and distinctly from other binding reagents

Detailed Description Paragraph Right (118):
One or more microfluidic guides may be used to prepare a plurality of binding domains on a fibril mat. Different or identical binding reagents may be present in a plurality of microfluidic guides and/or multiple distinct binding agents may be present in a microfluidic guide.

Detailed Description Paragraph Right (119):
In FIGS. 22A and 22B a plurality of microfluidic guides 2201, preferably in an array, are used to deliver, preferably concurrently, onto regions of the fibril mat 2200, drops containing the desired binding reagents, to form discrete binding domains 2202. The binding reagents form a bond with moieties present on the fibril mat. The binding reagents may adsorb non-specifically to the mat or dry on the surface.

Detailed Description Paragraph Right (145):
A plurality of fibril mats may be fabricated, preferably concurrently, and preferably in an array. In one example, an array of microfluidic guides forms a plurality of fibril mats on a support as described above. In another example, an array of filters, or a patterned filter (e.g., with regions of different porosity) is used to prepare an array of fibril mats.

Detailed Description Paragraph Right (207):
In a preferred embodiment, a cassette or apparatus of the invention comprises a means for sample delivery onto the plurality of discrete binding domains (see, e.g., element 1 on FIG. 1 of U.S. Pat. No. 5,147,806; element 1 on FIG. 1 of U.S. Pat. No. 5,068,088; each of which is incorporated by reference in its entirety). The means for sample delivery can be stationary or movable and can be any known in the art, including but not limited to one or more inlets, holes, pores, channels, pipes, microfluidic guides (e.g., capillaries), tubes, spigots, etc. Fluids can be moved through the system by a variety of well known methods, for example: pumps, pipettes, syringes, gravity flow, capillary action, wicking, electrophoresis, pressure, vacuum, etc. The means for fluid movement may be located on the cassette or on a separate unit. The sample can be placed on all of the binding domains together. Alternatively, a sample may be placed on particular binding domains by a capillary fluid transport means. Alternatively, samples may be placed on the support by an automatic pipetter for delivery of fluid samples directly to the PMAMS on a support, or into a reservoir in a cassette or cassette holder for later delivery directly to the binding surface.

Detailed Description Paragraph Right (270):
In a particular example of this aspect of the invention, binding domains, each of which have incorporated a different enzyme that utilizes as a substrate a sequential intermediate in a chemical reaction are situated on a PMAMS surface, such that the product of a given enzymatic reaction, which is the reactant for a subsequent enzyme, flows to the next enzyme in the reaction pathway. The invention also provides for bulk immobilization of enzymes on self-assembling monolayers, e.g., for industrial application, using methods as described above.

Detailed Description Paragraph Right (273):
In a preferred aspect of the use of PMAMS analogs to conduct non-ECL assays, drops of reaction medium are placed on a plurality of discrete domains, preferably delivered concurrently from an array of microfluidic guides; and then, optionally, to enhance stability and/or protect the drop, a more viscous solution (e.g., oil) is placed on top of the reaction medium or, alternatively, in between the discrete domain; and then sample containing an analyte to be detected or measured is applied to each domain, either by discrete application to each discrete domain or, in bulk, by exposing the entire surface of the PMAMS analog containing the domains to a fluid sample. Any resulting reaction in the binding domains is allowed to proceed, and the results are observed by use of a reporter and detection system selected from among those known in the art.

Detailed Description Paragraph Right (300):
The formation of PMAMS directly on the working electrode has several advantages over previous ECL systems: The combination of the working electrode and the solid phase support for the binding assays into one unit greatly simplifies the manufacture and execution of ECL assays in a disposable format, allowing disposable assays to be produced at lower cost. A plurality of assays can be performed without the use of

multiple ECL labels. The excitation of ECL from each of a plurality of assays can be conducted simultaneously by applying a potential to one working/counter electrode pair, all of the binding domains being located on the surface of the same working electrode). The use of the surface of a metal as the support for the PMAMS allows the use of well developed technology--e.g., the formation and patterning of self-assembled monolayers (SAMs) on metals--for the formation of the PMAMS.

Detailed Description Paragraph Right (303):
Binding reagents may be immobilized by non-specific adsorption directly to the electrode surface or by covalent attachment to a chemical functional groups on the surface of the electrode. One approach to the introduction of chemical functional groups on the surface of an electrode is electrodeposition or electropolymerization of thin films. Another approach is the preparation of self-assembled monolayers (SAMs). Examples of SAMs that can be prepared on electrode materials include monolayers of organic thiols on gold, and organic silanes on ITO (see Sec. 5.1). As shown in FIG. 50, a SAM may be prepared by the reaction of a molecule A-L-B 5032 with the surface of the electrode 5033, where A is the functional group responsible for the attachment of the molecule to the electrode, L is a linking chain, and B is a functional group which can be used for the attachment of binding reagents 5034 to the surface. Alternatively, B may be a binding reagent.

Detailed Description Paragraph Right (368):
PMAMS can be prepared on fibril mats. The reagents necessary to form the PMAMs are delivered to spatially distinct regions of a previously formed fibril mat by microfluidic guides as described previously. For example, an array of microfluidic guides (G1, G2, . . . Gn) can be used to deliver biotinylated antibodies (A1, A2 . . . An) to spatially distinct regions of a mat composed of streptavidin-coated fibrils. Derivatized fibrils may be delivered to spatially distinct regions of a support by microfluidic guides where they are captured, e.g. by filtration or evaporation. For example, an array of microfluidic guides (G1, G2, . . . Gn) can be used to deliver fibrils (F1, F2, . . . Fn) covalently linked to antibodies (A1, A2 . . . An) to spatially distinct regions of a gold-coated ultrafiltration membrane. In yet another method, a suspension of fibrils may be filtered through a physical mask, e.g. a wire mesh, placed in contact with a filter membrane so that fibrils deposit on the filter wherever the filter is exposed by the spaces between the wires of the mesh.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
204/400

Current US Cross Reference Classification (2):
204/403.15

Current US Cross Reference Classification (3):
422/50

Current US Cross Reference Classification (4):
422/52

Current US Cross Reference Classification (5):
422/55

Current US Cross Reference Classification (6):
422/61

Current US Cross Reference Classification (7):
422/82.05

Current US Cross Reference Classification (8):
422/82.07

Current US Cross Reference Classification (9):
422/82.08

Current US Cross Reference Classification (10):
435/287.1

Current US Cross Reference Classification (11):
435/287.2

Current US Cross Reference Classification (12):
435/288.7

Current US Cross Reference Classification (13):
435/808

Current US Cross Reference Classification (14):
435/810

Current US Cross Reference Classification (15):
435/968

Current US Cross Reference Classification (16):
435/975

Current US Cross Reference Classification (17):
436/164

Current US Cross Reference Classification (18):
436/172

Current US Cross Reference Classification (19):
436/518

Current US Cross Reference Classification (20):
436/524

Current US Cross Reference Classification (21):
436/534

Current US Cross Reference Classification (22):
436/805

Other Reference Publication (1):
Abbott and Whitesides, 1994, Potential-Dependent Wetting of Aqueous Solutions on Self-Assembled Monolayers Formed from 15-(ferrocenylcarbonyl) pentadecanethiol on Gold, Langmuir 10: 1493-1497.*

Other Reference Publication (5):
Bain and Whitesides, 1989, "Modeling Organic Surfaces with Self-Assembled Monolayers", Angew. Chem. 101: 522-528.*

Other Reference Publication (10):
DiMillia et al., 1994, "Wetting and Protein Adsorption of Self-Assembled (sic) Monolayers of Alkanethiolates Supported on Transparent Films of Gold," Journal of the American Chemical Society 116: 2225-2226.*

Other Reference Publication (32):
Pale-Grosdemange et al., 1991, "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo (ethylene Glycol) of Structure HS (CH2)11(OCH2CH2)m OH on Gold" Journal of the American Chemical Society 113: 12-20.*

Other Reference Publication (35):
Prime and Whitesides, 1993, "Adsorption of Proteins Onto Surfaces Containing End-Attached Oligo (ethylene oxide): A Model System Using Self-Assembled Monolayers" J. Amer. Chem. Soc. 115: 10714-721.*

Other Reference Publication (36):
Prime and Whitesides, 1991, "Self-Assembled Organic Monolayers; Model Systems for Studying Adsorption of Proteins at Surfaces", Science 252: 1164-1167.*

Other Reference Publication (45):
Wilber, et al., 1995, "Scanning Force Microscopies Can Image Patterned Self-Assembled Monolayers", Langmuir 11: 825-831.*

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

40. Document ID: US 6200761 B1

L23: Entry 40 of 94 File: USPT Mar 13, 2001

US-PAT-NO: 6200761
DOCUMENT-IDENTIFIER: US 6200761 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 40 of 94 File: USPT Mar 13, 2001

US-PAT-NO: 6200761
DOCUMENT-IDENTIFIER: US 6200761 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: March 13, 2001

US-CL-CURRENT: 435/6; 435/287.1, 435/287.2, 536/22.1, 536/23.1, 536/24.3

APPL-NO: 9/ 454497
DATE FILED: December 6, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This application is a continuing application of U.S. Ser. No. 09/306,749, filed May 7, 1999, which is a continuing application of 08/873,598, filed Jun. 12, 1997, U.S. Pat. No. 5,952,172, which is a continuing application of U.S. Ser. No. 08/660,534, filed Jun. 7, 1996, U.S. Pat. No. 5,770,369, which is a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995, U.S. Pat. No. 5,824,473, which is a continuing application of U.S. Ser. No. 08/166,036, filed Dec. 10, 1993, U.S. Pat. No. 5,591,578.

L23: Entry 40 of 94 File: USPT Mar 13, 2001

DOCUMENT-IDENTIFIER: US 6200761 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (1):
435/287.1

Current US Cross Reference Classification (2):
435/287.2

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

41. Document ID: US 6200737 B1

L23: Entry 41 of 94 File: USPT Mar 13, 2001

US-PAT-NO: 6200737
DOCUMENT-IDENTIFIER: US 6200737 B1

TITLE: Photodeposition method for fabricating a three-dimensional, patterned polymer microstructure

L23: Entry 41 of 94 File: USPT Mar 13, 2001

US-PAT-NO: 6200737
DOCUMENT-IDENTIFIER: US 6200737 B1

TITLE: Photodeposition method for fabricating a three-dimensional, patterned polymer microstructure

DATE-ISSUED: March 13, 2001

US-CL-CURRENT: 430/320; 422/82.06, 422/82.11, 430/321, 430/5

APPL-NO: 8/ 519062
DATE FILED: August 24, 1995

L23: Entry 41 of 94 File: USPT Mar 13, 2001

DOCUMENT-IDENTIFIER: US 6200737 B1
TITLE: Photodeposition method for fabricating a three-dimensional, patterned polymer microstructure

Brief Summary Paragraph Right (3):
Some reasonably defined and complex-patterned microstructures have been produced using differing techniques. For example, laser-assisted chemical vapor deposition ("LCVD") has been recently used to fabricate some complex well-defined microstructures [Wallenberger, F. T., Science 267: 1274-1275 (1995)]. Also, precision microstructures have been fabricated by the creation of hydrophobic templates from photoresists for the deposition of self-assembled monolayers ("SAMs") on gold [Gorman et. al., Chem. Mater. 7:252-254 (1995); Singhvi et. al., Science 264:696-698 (1994)]. In addition, photoactivation techniques have also been used to fabricate some well-defined

microstructures. As one representative example, photolithography has been used for information storage in photoconductive materials [Liu et. al. Science 261:897-899 (1993)]; in photoassembly of combinatorial libraries [Noble, D., Anal. Chem. 67:201A-204A (1995); Fodor et. al., Science 251: 767-773 (1991)]; and for site-selective covalent attachment of biomolecules [Yan et. al., J. Am. Chem. Soc. 115:814-816 (1993); Rozsnyai et. al., Angew. Chem. Int. Ed. Engl. 31:759-761 (1992)].

Detailed Description Paragraph Right (40):
Polymer micropatterns were also produced using a standard air force resolution target (chrome or glass) as the photopatterning mask in the assembly of FIG. 1. FIG. 9A shows a light micrograph of a partial air force resolution target. The image was taken through a 10.times. objective so that only the two middle groups could be observed. It is important to note that the mask has dimensions 15 times as large as those of the resulting microstructures fabricated by photodeposition, thereby facilitating the fabrication of complex micrometer-scale structures by relaxing the need to produce microscale masks.

Current US Cross Reference Classification (1):
422/82.06

Current US Cross Reference Classification (2):
422/82.11

42. Document ID: US 6197575 B1

L23: Entry 42 of 94 File: USPT Mar 6, 2001

US-PAT-NO: 6197575
DOCUMENT-IDENTIFIER: US 6197575 B1

TITLE: Vascularized perfused microtissue/micro-organ arrays

L23: Entry 42 of 94 File: USPT Mar 6, 2001

US-PAT-NO: 6197575
DOCUMENT-IDENTIFIER: US 6197575 B1

TITLE: Vascularized perfused microtissue/micro-organ arrays

DATE-ISSUED: March 6, 2001

US-CL-CURRENT: 435/288.4; 435/288.7, 435/297.5, 435/305.2, 435/33, 435/373, 435/395

APPL-NO: 9/ 272227
DATE FILED: March 18, 1999

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
Priority is claimed to U.S. provisional application Ser. No. 60/078,452, filed Mar. 18, 1998.

L23: Entry 42 of 94 File: USPT Mar 6, 2001

DOCUMENT-IDENTIFIER: US 6197575 B1
TITLE: Vascularized perfused microtissue/micro-organ arrays

Brief Summary Paragraph Right (1):
The present invention relates to microscale tissue arrays and their construction, where

the microscale tissue array is constructed from a micromatrix seeded with cells which forms a microtissue and/or a micro-organ, and to methods for using the microscale tissue arrays in a variety of systems and assays, for example, for determining the effect of biological and/or chemical agents on the microscale tissue arrays, or for detecting the presence of biological and/or chemical agents using microscale tissue arrays.

Brief Summary Paragraph Right (11):
A microscale tissue refers to a synthetically formed mass of cells forming a tissue structure or a structure that carries out tissue functions. As used herein, tissue refers to an aggregation of cells more or less similar morphologically and functionally; while a micro-organ includes cells of different morphology and/or function, such as hepatocytes and endothelial cells. The microscale tissue or organ unit contained in a single channel preferably is formed of less than about 10,000 cells, more preferably less than about 5,000 cells, and most preferably less than about 2,000 cells. The microscale tissue or organ unit contained in a single channel preferably is formed of at least about 150 cells. Microscale tissues (or micro-organs if formed of mixed cell types) may be combined to form multiunit tissue arrays. The density of channels in the array depends on the detection limits of the assay being performed, the size of the channels, and the materials of construction; preferable densities are at least 10-100 tissues/cm.sup.2, with the total number of channels determined by the mass or number of cells required for a particular assay. A microscale tissue array refers to an array of synthetically fabricated microscale tissues. The array preferably contains at least about 4 microscale tissues, more preferably at least about 50 microscale tissues, but may contain only one channel if the readout is sensitive to the number of cells contained in a single channel.

Brief Summary Paragraph Right (12):
The system can be used to screen materials for an effect on the cells, for an effect of the cells on the materials (for example, in a manner equivalent to tissue metabolism of a drug), to test a material on a biological that must first infect cells or tissues, such as viruses, to expand a biologic or unique cell population, such as stem cells, or to provide an environment for gene therapy. The microscale tissue arrays are particularly useful for the study of many phenomena, including clearance, metabolism, activation, transport, and bioavailability of xenobiotics, including drug candidates. The microscale tissue arrays can also be used to study toxicity, teratogenicity, genotoxicity, carcinogenicity, and mutagenicity, in terms of basal, local, and/or organ-specific impact, under conditions of acute or chronic exposure. The microscale tissue arrays can be used to construct disease models, for use in studies on the impact of chemical and/or biological agents on the course of the disease. The microscale tissue arrays can be used to detect the presence of infectious agents, as well as chemical and biological weapons. The microscale tissue arrays can also be used for dose ranging studies for drug candidates.

Brief Summary Paragraph Right (13):
The results from these studies can be entered into mathematical models to predict the response of organs in vivo. The results can also be entered into mathematical models to predict pharmacokinetics and/or pharmacodynamics of chemical and biological agents. The systems employing the microscale tissue arrays can be integrated with other test systems, such as those which concern genomics, gene transcription, protein expression, and other biological phenomena of interest. In comparison to test systems using whole organs, test systems using microscale tissue arrays provide results at far less expense per test. In comparison to test systems using tissue slices and cells, test systems using microscale tissue arrays provide results at comparable expense per test; however, the results are more relevant to human health, as the cells in the microscale tissue array maintain high viability, phenotype, and differentiated function.

Drawing Description Paragraph Right (5):
FIGS. 5A and 5B are schematics of an apparatus for using microscale tissue arrays as part of a high-throughput batch system for chemical and biological testing, wherein a microscale tissue array is placed in each well of a multi-well plate (FIG. 5A), and wherein the multi-well plate is placed on top of a vacuum box (FIG. 5B).

Drawing Description Paragraph Right (7):
FIG. 7 is a process flow diagram showing an apparatus for using a microscale tissue array as part of a continuous flow system for chemical and biological testing.

Drawing Description Paragraph Right (9):
FIG. 9 is a graph illustrating the correlation coefficient between an in vivo test and

the prediction from a microscale organ test.

Drawing Description Paragraph Right (10):
FIG. 10 is a schematic of an array of microscale tissue arrays.

Detailed Description Paragraph Right (3):
The functional unit of the matrix are channels. These are typically between 75 and 400 .mu.m in diameter. In the preferred embodiments, the matrix is a micromatrix, although the dimensions can range from nanometers to millimeters. The array will typically have a cross-sectional area of a few square centimeters or less, preferably 1 square centimeter or less. The depth of the array will typically be less than 1 centimeter, preferably 1 mm or less. These same size considerations apply to arrays of microscale tissues for test purposes.

Detailed Description Paragraph Right (4):
The channels are seeded with cells which form tissue within the channel, or which form aggregates or spheroids suspended or maintained within the channels. Each layer of matrix containing channels within a single plane is referred to as a microtissue. These "microtissues" can be either tissues, i.e. formed of functionally similar cells, or organs, i.e. formed of a mixture of cells having different functions and/or phenotypes. For convenience, both terms are referred to as "microtissue" unless otherwise noted. Microtissues are layered together to form microscale tissue or micro-organ arrays. The arrays can consist of tissues stacked on top of each other, side by side each other, or both. They may be interconnected or isolated. In the preferred embodiment, an organ is formed in each channel, wherein each channel contains several cell types with different functions. The primary reason they are in individual channels is that they will not form appropriate tissue structures over large length scales. The number of cells which will form a tissue/organ structure is fixed and thus the mass of cells needed for a particular assay is obtained by scaling the number of each micro-organ in the total array. The microscale tissue preferably is formed of less than about 10,000 cells, more preferably less than about 5,000 cells, and most preferably less than about 2,000 cells. The microscale tissue preferably is formed of at least about 150 cells, although the micromatrix may be seeded with as few as 25 to 50 cells. A microscale tissue array refers to an array of synthetically fabricated microscale tissues, preferably at least about 4 microscale tissues, more preferably at least about 50 microscale tissues.

Detailed Description Paragraph Right (5):
The type(s) of cells determine the function of the tissue. As used herein, tissue refers to an aggregation of cells more or less similar morphologically and functionally. In one embodiment, the matrix is seeded with a mixture of cells including endothelial cells and at least one type of parenchymal cells, such as hepatocytes, pancreatic cells, or other organ cells, or the matrix is seeded with totipotent/pluripotent stems cells which can differentiate into cells, including endothelial cells to form a micro-organ. Mixtures of cells of diverse function are referred to as micro-organs. With either approach, the endothelial cells (and in some cases other cells such as pericytes or stellate cells) will form "blood vessels" throughout the tissue. An organ refers to a differentiated structure of an organism composed of various cells or tissues and adapted for a specific function (McGraw-Hill Dictionary of Bioscience). As used herein, a microscale organ refers to a microscale tissue, or combination of microscale tissues, which exhibits at least one function or characteristic of a particular organ, at an representative, specific level. Specific level refers to absolute level per unit of scale, such as level per cell number, volume, mass, or surface area, considering only the cellular compartments, not the substrate. The cross-sectional area is typically less than 1 cm.sup.2, and the depth is typically less than 0.5 cm. For example, in terms of the function of xenobiotic biotransformation, a microscale liver would transform a xenobiotic at a specific rate representative of a whole liver, where the specific rate might be measured in moles per unit time and cell volume. In terms of the characteristic of susceptibility to viral hepatitis infection, a microscale liver would exhibit a time course of infection representative of a whole liver, when infected with the same number of viral particles per cell or per cell surface area. The required degree of cell representation will depend on the particular user requirements. In certain circumstances, specific levels which are representative of the actual organ within an order of magnitude may be sufficiently accurate. In other circumstances, the specific levels may need to be within 10% or less of the actual organ levels. Sufficient accuracy over extended duration of testing will be critical for certain tests. Qualification studies will generally be performed with arrays of microscale tissue. If the compounds yield the desired results with the arrays, they are then screened using arrays of microscale organs.

Detailed Description Paragraph Right (6):
A microscale organ mimicking liver function or characteristics is useful for monitoring drug clearance, production of metabolites, activation of prodrugs, capture of asiolo proteins, and susceptibility to toxins or acute or chronic infection.

Detailed Description Paragraph Right (7):
High throughput screening can be carried out by preparing multiwell plates, and inserting microscale organs in each well. Different drugs can be evaluated simultaneously by adding different drugs to each well. The microscale organs can also be used in a differential bioreactor system. The reactor includes one or more microscale organs and means for maintaining the viability of the organs, for example, a supply of oxygen and nutrients. Sensors for following the metabolism of the agents can be present. Preferably, the reactor can be equipped with a computer to control, for example, the supply of oxygen and nutrients and the collection, analysis and purification of samples. Metabolites of the agents can be prepared and isolated by administering various agents to the bioreactor. In one embodiment, the microscale organ is sandwiched between filters which prevent passage of the organ but which allow passage of the metabolites. A steady stream of fluids, for example, blood, through the organ can remove the metabolites in a continuous manner. The metabolite can be extracted from the fluid and the fluid recycled through the organ. This represents a continuous process for preparing metabolites using the microscale organs. The reactor can be operated in a one-pass mode, a recirculating mode, or combination thereof.

Detailed Description Paragraph Right (8):
Microscale organs can be used to monitor the effect of exposure of the organs to various therapeutic agents. If the organ is challenged in such a way that it can react to an effective dose of the therapeutic agent, the minimum effective dose can be calculated. Further, as the dose is increased, one can determine the maximum tolerated level. Accordingly, both dosage and efficacy can be measured using the microscale organs described herein.

Detailed Description Paragraph Right (9):
The potential benefits of monitoring the exposure of the microscale organs to various therapeutic agents is that faster, cheaper secondary screens can be developed, which represent actual human organs, and which may be used in new disease models. This offers a potential reduction in animal testing and also offers testing on actual human tissue without subjecting human test patients to untested drugs. The microscale organs also offer an opportunity to test drugs in which no animal model is adequate.

Detailed Description Paragraph Right (10):
The results from tests with microscale organs can be entered into appropriate scale-up models to predict the response of whole organs in vivo. Tests can furthermore be performed using a series of microscale organ arrays, arranged so as to provide a scale down model of an organ system. The results can be scaled-up to predict the response of the organ system in vivo or an entire organism, such as a human.

Detailed Description Paragraph Right (11):
In some embodiments, the apparatus is used for in vitro analyses, for example, high throughput screenings of chemical and biological agents. In other embodiments, the apparatus is used as a bioreactor to produce chemical or biological agents. In other embodiments, the apparatus is used to generate hard-to-produce cells and tissue, such as stem cells. In still further embodiments, the apparatus is used to generate cells for implantation, optionally after the cells have been transfected. Examples of the apparatuses include micro-tissue devices, micro-scale organs, bioreactors and high throughput screening systems.

Detailed Description Paragraph Right (13):
Test systems using microscale tissue arrays have a broad range of uses, including, but not limited to, studies on biotransformation, clearance, metabolism, and activation of xenobiotics; studies on bioavailability and transport of chemical agents across epithelial layers; studies on bioavailability and transport of biological agents across epithelial layers; studies on transport of biological or chemical agents across the blood-brain barrier; studies on acute basal toxicity of chemical agents; studies on acute local or acute organ-specific toxicity of chemical agents; studies on chronic basal toxicity of chemical agents; studies on chronic local or chronic organ-specific toxicity of chemical agents; studies on teratinogenicity of chemical agents; studies on genotoxicity, carcinogenicity, and mutagenicity of chemical agents; detection of infectious biological agents and biological weapons; detection of harmful chemical

agents and chemical weapons; studies on infectious diseases; studies on the efficacy of chemical agents to treat disease; studies on the efficacy of biological agents to treat disease; studies on the optimal dose range of agents to treat disease; prediction of the response of organs in vivo to biological agents; prediction of the pharmacokinetics of chemical or biological agents; prediction of the pharmacodynamics of chemical or biological agents; studies concerning the impact of genetic content on response to agents; filter or porous material below microscale tissue may be chosen or constructed so as bind denatured, single-stranded DNA; studies on gene transcription in response to chemical or biological agents; studies on protein expression in response to chemical or biological agents; studies on changes in metabolism in response to chemical or biological agents; prediction of agent impact through database systems and associated models; prediction of agent impact through expert systems; and prediction of agent impact through structure-based models.

Detailed Description Paragraph Right (27):
Scaffolds can be produced by etching single-side polished silicon wafers of standard thicknesses followed by grinding and polishing to reduce the wafer thickness to 150 to 400 .mu.m. Alternatively, etch through microchannels can be fabricated in thin, double-side polished wafers of desirable target thickness. In this case, no further grinding and polishing is necessary. During etching, the active thin wafers can be mounted with photoresist to quartz handle wafers, facilitating end etch point determination. The photoresist can be applied to the whole surface of the handle wafer or only to its perimeter. Discs of 1.5 to 2 cm diameter can be produced with the appropriate array of channels in each; with the current design, seven scaffolds can be produced from each wafer, with relatively large features compared to standard Si microfabrication. This allows one to make photolithography masks by printing designs on high resolution (3386 dpi) photographic film. This flexibility in mask production allows us to produce masks much more cheaply and quickly than the standard chrome-on-glass approach and thus to test many different channel geometries.

Detailed Description Paragraph Right (31):
To ensure cell adhesion preferentially in the channels, the upper surface of the silicon substrate can be coated with an ethylene oxide-based film using silane chemistry to couple the organic material to the oxide surface. Other treatments can also be used to enable bonding of a second wafer to the first water. This derivatization can be performed selectively on the outer surface of the wafer as the presence of the fluoropolymer materials on the walls of the channels will prevent attachment to this location. Reacting between chemically synthesized CH.sub.3 (OCH.sub.2 CH.sub.2).sub.3 O(CH.sub.2).sub.11 SiCl.sub.3 and the oxide surface can be used to produce self-assembled monolayer films that are known to passivate silicon substrates against the adsorption of many types of adventitious species. With this silane, the reaction proceeds to anchor an oriented molecular film on the oxide surface and expose ethylene oxide groups to the surrounding environment. For channels produced using KOH as the etchant, the channels and top surface can be first treated with CH.sub.3 (CH.sub.2).sub.17 SiCl.sub.3 to coat the channels and outer surface with alkyl chains to make the surface hydrophobic. The outer surface can be selectively cleaned using applied UV/O.sub.2 treatments at a grazing angle to minimize decomposition of coated regions within the channel or the use of aqueous cleaning solutions that will be prevented from entering the channels due to capillary forces that restrict penetration of the aqueous solution into the hydrophobic channels. For these cases, the exposed cleaned surface can be made non-adsorbing by reaction with CH.sub.3 (OCH.sub.2 CH.sub.2).sub.3 O(CH.sub.2).sub.11 SiCl.sub.3 that will again form a layer selectively on the outer surface due to the presence of the hydrophobic film within the channel areas.

Detailed Description Paragraph Right (113):
FIG. 5A is a schematic illustration of an apparatus for using microscale tissue arrays as part of a high-throughput batch system for chemical and biological testing. A microscale tissue array 101 is placed in each well 102 of a multi-well plate 103. The microscale tissue arrays may be held above the bottom of the wells through ridges or slots in each well. The bottom 104 of each well may consist of solid material, such as glass or plastic, filter material, such as nylon, cellulose, nitrocellulose, or PVDF, or porous material, such as porous glass or porous silicon. Culture medium or test fluid is in direct contact with the top of the microscale tissue array and permeates the tissue array.

Detailed Description Paragraph Right (114):
105 is in direct contact with the top of the microscale tissue array and permeates the tissue array. If the microscale tissue array is held off the bottom of the well, a

certain volume of culture medium or test fluid 105a will occupy the space between the microscale tissue array and the bottom of the well. The gas phase compositions above the multi-well plate can be adjusted so as to provide the appropriate oxygen, pH, and carbon dioxide levels throughout the microscale tissue arrays.

Detailed Description Paragraph Right (115):
FIG. 5B is a schematic illustration of an apparatus for using microscale tissue arrays as part of a high-throughput batch system for chemical and biological testing, wherein the multi-well plate 115 is placed on top off a vacuum box 114. A microscale tissue array 101 is placed in each well of the multi-well plate. The microscale tissue arrays may be held above the bottom of the wells through ridges or slots in each well. The bottom 117 of each well may consist of filter material, such as nylon, cellulose, nitrocellulose, or PVDF, or porous material, such as porous glass or porous silicon. As in FIG. 5A, culture medium or test fluid is in direct contact with the top of the microscale tissue array and permeates the tissue array. If the microscale tissue array is held off the bottom of the well, a certain volume of culture medium or test fluid will occupy the space between the microscale tissue array and the bottom of the well.

Detailed Description Paragraph Right (116):
In FIG. 5B, the vacuum box is configured with a gas inlet 111 and a gas outlet 112. A vacuum may be applied to the gas outlet, such that the fluid surrounding each microscale tissue array is brought through each well bottom, down through a funnel 118, and into the corresponding well 119 of a multi-well collection plate 113. Gas may be subsequently added to the vacuum box through gas inlet 111, providing a target gas phase composition and pressure in the box. The gas phase composition and pressure may be different than that of gas phase above the multi-well plate with the microscale tissue arrays. The gas phase compositions can be adjusted so as to provide the appropriate oxygen, pH, and carbon dioxide levels throughout the microscale tissue arrays.

Detailed Description Paragraph Right (117):
FIG. 6A is a schematic illustration of an apparatus for using microscale tissue arrays as part of a high-throughput flow system for chemical and biological testing, wherein the multi-well plate 142 is placed on top of a vacuum box 144 and a manifold system 140 is used to deliver fluid to each well at frequent intervals. A microscale tissue array 101 is placed in each well of the multi-well plate. The microscale tissue arrays may be held above the bottom of the wells through ridges, slots, or adhesive agent in each well. Filter material, such as nylon, cellulose, nitrocellulose, or PVDF, porous material, such as porous glass or porous silicon, or screens, such as metal screens, may be placed above 146 or below 147 each microscale tissue array. As in FIG. 5A, culture medium or test fluid is in direct contact with the top of the microscale tissue array and permeates the tissue array. If the microscale tissue array is held off the bottom of the well, a certain volume of culture medium or test fluid will occupy the space between the microscale tissue array and the bottom of the well.

Detailed Description Paragraph Right (118):
In FIG. 6A, the vacuum box is configured with a gas inlet 155 and a gas outlet 145. A vacuum may be applied to the gas outlet, such that the fluid surrounding each microscale tissue array is brought through each well bottom, down through a funnel 148, and into the corresponding well 149 of a multi-well collection plate 143. Gas may be subsequently added to the vacuum box, providing a target gas phase composition and pressure in the box. The gas phase composition and pressure may be different than that of gas phase above the multi-well plate with the microscale tissue arrays. The gas phase compositions can be adjusted so as to provide the appropriate oxygen, pH, and carbon dioxide levels throughout the microscale tissue arrays.

Detailed Description Paragraph Right (119):
In FIG. 6A, a manifold system 140 is used to deliver culture medium or test fluid to each well at frequent intervals. The fluid is delivered to each well through a small pipe or pipette tip 141. The fluid delivery system can be operated in concert with the vacuum system, such that the fluid volume in each well of the multi-well plate 142 is maintained constant or within an acceptable range. Fluid may be delivered across a broad range of intervals, such as from once per day to a few times per second. Appropriate flow conditions can be derived through design of the well geometry in the multi-well plate 142, selection of materials above 146 and below 147 the microscale tissue arrays based on flow resistance properties, design of the microscale tissue devices based on flow resistance properties, and design of the manifold and vacuum systems.

Detailed Description Paragraph Right (120):
In FIG. 6A, the multi-well collection plate 143 can be removed from the vacuum box once fluid surrounding the microscale tissue arrays has been collected. The fluid in the collection plate can then be assayed and/or, through the use of the manifold delivery system, recycled back through the microscale tissue array from whence it came. When a collection plate with fluid is removed from the vacuum box, an empty collection plate can placed in the appropriate position in the box, ready to collect the fluid from the next flow cycle.

Detailed Description Paragraph Right (121):
FIG. 6B is identical to FIG. 6A, except that an array of sensors 151 is used to detect events in each well. The signal from each sensor is sent through information lines 152 to a information display or processing device 150, such as a computer. Each sensor may consist of miniaturized fiber optic system, which provides single or multi-photon excitation to each microscale tissue and detects the resulting fluorescent intensity from the microscale tissue array. Other sensors may be used, such as ones which detect fluorescence, luminescence, or light absorption. Material with appropriate optical properties can be selected for use above 146 and below 147 the microscale tissue array. A large light source, or array of microscale light sources, can be placed within or below the vacuum box, such that each microscale tissue array is exposed to light from below. The tip of each sensor may be placed into the fluid above each microscale tissue array. Sensors which detect oxygen, pH, CO.sub.2, or some other chemical entity may then be used. Sensors in the fluid above each microscale tissue array may also be used which detect the resistance to electron flow across the microscale tissue array. In this case, a miniature cathode or anode may extend into the fluid below each microscale tissue to complete a circuit with the respective sensor above the array.

Detailed Description Paragraph Right (122):
In FIGS. 5A, 5B, 6A, and 6B, the composition of the filter, porous, or screen materials above or below the microscale tissue array should be selected so as to not bind particular chemical compounds or classes of compounds. The materials should not bind test compounds under study, their resulting metabolites, or key components of the culture medium, such as growth factors. Under many conditions, a filter composed of PVDF material fulfills this requirement. The materials may need to be precoated with certain compounds, such as albumin or collagen.

Detailed Description Paragraph Right (123):
In FIGS. 5A, 5B, 6A, and 6B, the filter, porous, or screen materials below the microscale tissue array can be used which bind particular chemical compounds or classes of compounds. The materials may be such chosen or constructed so as to bind DNA molecules, DNA molecules with a particular sequence or sequences, RNA molecules, RNA molecules with a particular sequence or sequences, protein molecules, protein molecules with a particular composition or binding activity, and other biological molecules of interest. These molecules can then be captured from the fluid surrounding the microscale tissue arrays as it brought down into the collection plate through the vacuum operation. Alternatively, or in addition, these molecules can be extracted from the microscale tissue array in each well, according to standard extraction methods well known to those skilled in the art, and then captured from the extraction solution as it is brought down into the collection plate through the vacuum operation. Tests can then be performed to quantify or characterize the captured molecules.

Detailed Description Paragraph Right (124):
FIG. 7 is a schematic illustration of an apparatus for using a microscale tissue array 101 as part of a continuous flow system for chemical and/or biological testing. Culture medium containing a test substance is circulated by a pump 186 through a microscale tissue array 101 contained within a reactor housing 181. The circulation rate can be controlled by a computer 183 connected to the circulation pump. The fluid recycles around a continuous flow loop 201 which, if necessary for gas exchange, can contain a flow-through oxygenator 187 which supplies oxygen and removes carbon dioxide. In certain circumstances, gas exchange through the walls of the loop tubing may be sufficient to eliminate the need for the oxygenator. The oxygenator contains gas permeable tubing, in sufficient quantity to allow for the required gas exchange with the oxygenator inlet gas 190. Oxygen transfers from the gas into the medium, while carbon dioxide transfers from the medium into the gas and is carried away as part of the exit gas 191. The flow rate of the inlet gas can be controlled through the use of a control valve 192 connected to a computer control system 183.

Detailed Description Paragraph Right (125):
In FIG. 7, the composition of the circulating medium can be assessed through the use of

sensors upstream 192 and/or downstream 194 of the microscale tissue array. Numerous sensors may be used at either position, including sensors which measure oxygen, pH, glucose, carbon dioxide, test substances, metabolites of test substances, or other critical biological parameters. A reactor sensor 193 can be used which penetrates through the reactor housing. The reactor sensor may consist of miniaturized fiber optic system, which provides single or multi-photon excitation to each microscale tissue and detects the resulting fluorescent intensity from the microscale tissue array. Other sensors may be used, such as ones which detect fluorescence, luminescence, light absorption, or the resistance to electron flow across the microscale tissue array.

Detailed Description Paragraph Right (128):
Alternatively, a control scheme may be implemented to provide a target profile of reaction rate versus time for a reaction occurring in the microscale tissue array. The rate could be assessed continuously through the use of the upstream and downstream sensors. The continuous flow system depicted in FIG. 7 is highly flexible and can be operated according to a wide variety of control schemes.

Detailed Description Paragraph Right (129):
FIG. 9 illustrates a set of results from a validation study concerning the qualification of a microscale tissue array as a microscale organ array. In such a study, the effect of a chemical or biological agent on a particular characteristic of a microscale tissue array is determined through the use of an appropriate test system, such as those illustrated in FIGS. 5A, 5B, 6A, 6B, or 7. The results from the test are entered in to an appropriate scale-up model to predict the effect of the agent on an organ in vivo. The prediction is then compared to the result from a separate study which determines the effect of the agent on the particular characteristic of an isolated organ perfused in vivo. The microscale tissue test, corresponding prediction and corresponding in vivo assessment are performed across a range of agent concentrations and/or compositions. The results are plotted on a graph, as shown in FIG. 9, and the concordance correlation coefficient is determined. If the concordance correlation coefficient is near 1 or at least above an acceptable lower limit, the microscale tissue array used in the respective test system qualifies as a microscale organ array for the particular characteristic tested.

Detailed Description Paragraph Right (130):
FIG. 10 is an array of microscale tissue arrays. A series of microscale tissue arrays was constructed out of a single piece of substrate 300, which may be made of, but not limited to, silicon, polymeric material, or other suitable materials. The resulting fabrication can be placed, with appropriate gaskets, into a housing with multiple chambers such that each microscale tissue array 101 is contained within a well. Filter material, porous material, or screens may be incorporated into the housing so as to occupy a position above and/or below each microscale tissue array. The resulting device is analogous to a multi-well plate and can be used in systems such as those shown in FIGS. 5A, 5B, 6A, or 6B.

Detailed Description Paragraph Right (133):
Test systems using microscale tissue arrays have a broad range of uses for in vitro assays. Using the arrays, one can study biotransformation, clearance, metabolism, and activation of xenobiotics. The bioavailability and transport of chemical and biological agents across epithelial layers and across the blood-brain barrier can be studied. The acute basal toxicity, acute local toxicity or acute organ-specific toxicity, teratogenicity, genotoxicity, carcinogenicity, and mutagenicity, of chemical agents can also be studied. Infectious biological agents, biological weapons, harmful chemical agents and chemical weapons can be detected. Infectious diseases and the efficacy of chemical and biological agents to treat these diseases, as well as optimal dosage ranges for these agents, can be studied. The response of organs in vivo to chemical and biological agents, and the pharmacokinetics and pharmacodynamics of these agents can be predicted. The impact of genetic content on response to the agents can be studied.

Detailed Description Paragraph Right (136):
Filter or porous material below microscale tissue may be chosen or constructed so as bind denatured, single-stranded DNA. Nitrocellulose filters can be used in this manner. The captured DNA can then be characterized through hybridization techniques using oligonucleotide probes. Alternatively, the filter or porous material may contain immobilized probes which capture denatured, single stranded DNA with specific sequences. The captured DNA may be analyzed in place or after subsequent release, and may be amplified through PCR or other similar techniques. Alternatively, the microscale tissue may be contained in each sample well of a flowthrough genosensor. These genosensors are illustrated on page 218 of Doktycz, et al., "Genosensors and Model

Hybridization Studies" in Automation Technologies for Genome Characterization, T. J. Beugelsdijk, ed. (John Wiley & Sons, New York 1997).

Detailed Description Paragraph Right (137):
Filter or porous material below microscale tissue may be chosen or constructed so as to bind RNA. Chemically-treated cellulose filters, nylon filters, and under certain circumstances, nitrocellulose filters, fulfill this requirement. The captured RNA can then be characterized through hybridization techniques using oligonucleotide probes. Alternatively, the filter or porous material may contain immobilized probes which capture denatured, single-stranded RNA with specific sequences. The captured RNA may be analyzed in place or after subsequent release, and may be amplified through PCR or other similar techniques. Alternatively, the microscale tissue may be contained in each sample well of a flowthrough genosensor. These genosensors are illustrated on page 218 of Doktycz, et al., "Genosensors and Model Hybridization Studies" in Automation Technologies for Genome Characterization, T. J. Beugelsdijk, ed., (John Wiley & Sons, New York 1997).

Detailed Description Paragraph Right (159):
An example of a suitable bioreactor is shown in FIG. 11. In the bioreactor 300, a microscale organ 302 is provided, along with an oxygenator 304, a reservoir 306 providing nutrient medium 308, and a sample of an agent 310 to be processed by the organ. The medium and the agent are pumped through the organ, and samples collected as desired. Various sensors 312 are included at different portions of the loop. The system is controlled by a computer 314.

Detailed Description Paragraph Right (185):
A cross-flow bioreactor was developed as described above and tested. Two fabrication methods were used. In the first fabrication route, the microchannels were microfabricated in silicon while the housing of the bioreactor was machined in stainless steel using standard machining. This design was used for the initial proof-of-the-principle laboratory testing. The second fabrication route incorporating anodic bonding provided means for large volume production of bioreactors.

Detailed Description Paragraph Right (189):
The scaffold providing support for cell attachment and growth, as well as perfusion with nutrient and oxygen, is made out of silicon using a highly anisotropical deep reactive ion etching. The same etch through process employed to form microchannels also is used to cut the silicon wafer into individual disks without increasing the number of processing steps. Dicing the wafer into individual devices is thereby eliminated. This approach offers high flexibility, but its machining (a serial process) is costly. Alternatively, the cost of the perfusion bioreactor can be significantly reduced by using batch microfabrication techniques. These parallel techniques can yield inexpensive and disposable cartridge-like bioreactors. In one approach, these bioreactors can be built from silicon and glass wafers bonded together. For example, scaffolds with microchannels and perforated or porous screens can be microfabricated in a silicon wafer. The microchannels can be encapsulated by anodically bonding Pyrex (e.g. 7740) borosilicate wafers to the upper and lower surfaces of the silicon wafer (Wallis & Pomerantz, J. Appl. Physics 40: 3946 (1969)). Besides encapsulation, the top Pyrex wafer provides the same functions as the optically transparent disk described above. The bottom Pyrex wafer allows backside illumination of the microchannels, if necessary. Bonding can be accomplished on a hot plate in atmosphere or vacuum at temperatures and voltages typically between 180 and 500.degree. C. and 200 to 1000V, respectively (Madou, Fundamentals of Microfabrication (CRC Press 1997)). A pressure usually is applied to force the wafers together during bonding. The coefficients of thermal expansion of silicon and Pyrex are closely matched. This is critical not only for the bonding process but also for rapid cryopreservation of tissues structures. Prior to anodic bonding, large conducting channels parallel to the wafer surface can be etched in Pyrex, which can be done, for example, in HF solution. These channels can be coupled to the outer environment by etched or ultrasonically (or laser) drilled holes. The aniodic bonding technique will preserve the features both in silicon and Pyrex. Since features in both silicon and Pyrex are present, precise alignment of the silicon and Pyrex wafers is mandatory. This task can be accomplished, for example, using an Electronic Visions/Aligner Bonder (available in Microtechnology Technology Laboratories at the Massachusetts Institute of Technology). After bonding, the stack of Pyrex and silicon wafers can be diced into individual die. Depending on the application, the die can contain a desirable number of completely isolated microchannel arrays, each array having its own input and output. Therefore, an array of bioreactors can be fabricated on a single chip.

Current US Original Classification (1):
435/288.4

Current US Cross Reference Classification (1):
435/288.7

Current US Cross Reference Classification (2):
435/297.5

Current US Cross Reference Classification (3):
435/305.2

Current US Cross Reference Classification (4):
435/33

Current US Cross Reference Classification (5):
435/373

Current US Cross Reference Classification (6):
435/395

43. Document ID: US 6193866 B1

L23: Entry 43 of 94 File: USPT Feb 27, 2001

US-PAT-NO: 6193866
DOCUMENT-IDENTIFIER: US 6193866 B1

TITLE: Separation of charged particles by a spatially and temporally varying electric field

L23: Entry 43 of 94 File: USPT Feb 27, 2001

US-PAT-NO: 6193866
DOCUMENT-IDENTIFIER: US 6193866 B1

TITLE: Separation of charged particles by a spatially and temporally varying electric field

DATE-ISSUED: February 27, 2001

US-CL-CURRENT: 204/450; 204/600

APPL-NO: 9/ 212622
DATE FILED: December 16, 1998

PARENT-CASE:

This is a continuation-in-part of U.S. patent application Ser. No. 08/623,346, filed Mar. 27, 1996, now U.S. Pat. No. 5,938,904 which is incorporated by reference herein in its entirety.

L23: Entry 43 of 94 File: USPT Feb 27, 2001

DOCUMENT-IDENTIFIER: US 6193866 B1
TITLE: Separation of charged particles by a spatially and temporally varying electric field

Detailed Description Paragraph Right (120):

A second alternative method suitable for Au uses micro-contact printing (.mu.CP) (Xia et al., 1995, J Am. Chem. Soc. 117:3274-3275; Jackman et al., 1995, Science 269:664-666). Instead of a photolithography mask, an elastomeric stamp made according to an identical pattern of the same dimensions is used. FIGS. 16A-B illustrate exemplary patterns. The stamp can be fabricated from polydimethylsiloxane. As before, Au is deposited to a thickness of 1 .mu.m on the surface of the substrate using standard methods. Next, the elastomeric stamp is wetted with an alkanethiol and pressed against the gold surface. A suitable alkanethiol is CH.sub.3 (CH.sub.2).sub.15 SH (Kumar et al., 1994, Langmuir 10: 1498-1511). Controlled spreading of the patterned self-assembled alkanethiol monolayer on the gold surface can be achieved by performing the printing under water, which has the further benefit of shrinking the feature size in a predictable manner. The stamp and substrate are removed from the water and dried using N.sub.2 gas, and then the stamp is removed from the substrate. Unprotected gold is removed by immersion in a cyanide solution (0.1 M KCN, 1 M KOH) with vigorous stirring using air or oxygen as an oxidant (Kumar et al., supra.). After a good rinse, the alkanethiol is removed from the surface to yield the pluralities of gold electrodes.

Current US Original Classification (1):
204/450

Current US Cross Reference Classification (1):
204/600

Other Reference Publication (36):
Jacobson et al., No month available 1994, "Effects of injection schemes and column geometry on the performance of microchip electrtophoreis devices", Anal. Chem. 66:1107-1113.

44. Document ID: US 6180352 B1

L23: Entry 44 of 94 File: USPT Jan 30, 2001

US-PAT-NO: 6180352
DOCUMENT-IDENTIFIER: US 6180352 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 44 of 94 File: USPT Jan 30, 2001

US-PAT-NO: 6180352
DOCUMENT-IDENTIFIER: US 6180352 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 435/6; 536/23.1, 536/24.3

APPL-NO: 9/ 459191
DATE FILED: December 10, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This application is a continuing application of U.S. Ser. No. 09/306,749, filed May 7, 1999, which is a continuing application of Ser. No. 08/873,598, filed Jun. 12, 1997, U.S. Pat. No. 5,952,172, which is a continuing application of U.S. Ser. No. 08/660,534, filed Jun. 7, 1996, U.S. Pat. No. 5,770,369, which is a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995, U.S. Pat. No. 5,824,473, which is a continuing application of U.S. Ser. No. 08/166,036, filed Dec. 10, 1993, U.S. Pat. No. 5,591,578.

L23: Entry 44 of 94 File: USPT Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180352 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

45. Document ID: US 6177250 B1

L23: Entry 45 of 94 File: USPT Jan 23, 2001

US-PAT-NO: 6177250
DOCUMENT-IDENTIFIER: US 6177250 B1

TITLE: Nucleic acid mediated electron transfer

L23: Entry 45 of 94 File: USPT Jan 23, 2001

US-PAT-NO: 6177250
DOCUMENT-IDENTIFIER: US 6177250 B1

TITLE: Nucleic acid mediated electron transfer

DATE-ISSUED: January 23, 2001

US-CL-CURRENT: 435/6; 536/23.1, 536/24.3

APPL-NO: 9/ 306737
DATE FILED: May 7, 1999

PARENT-CASE:

CROSS REFERENCE TO RELATED APPLICATIONS
This is a continuing application of U.S. Ser. No. 08/660,534, filed Jun. 7, 1996, now U.S. Pat. No. 5,770,369, which is a continuing application of U.S. Ser. No. 08/475,051, filed Jun. 7, 1995, now U.S. Pat. No. 5,827,473, which is a continuing application of U.S. Ser. No. 08/166,036, filed Dec. 10, 1993, now U.S. Pat. No. 5,591,578.

L23: Entry 45 of 94 File: USPT Jan 23, 2001

DOCUMENT-IDENTIFIER: US 6177250 B1
TITLE: Nucleic acid mediated electron transfer

Current US Original Classification (1):
435/6

Other Reference Publication (14):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubtituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (69):
Palecek, "From Polarography of DNA to Microanalysis with Nucleic Acid-Modified Electrodes," Electroanalysis. 8(1):7-14 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Suface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

46. Document ID: US 6169194 B1

L23: Entry 46 of 94 File: USPT Jan 2, 2001

US-PAT-NO: 6169194
DOCUMENT-IDENTIFIER: US 6169194 B1

TITLE: High surface density covalent immobilization of oligonucleotide monolayers using a 1-(thiotrifluoroacetato)-11-(trichlorososilyl)-undecane linker

L23: Entry 46 of 94 File: USPT Jan 2, 2001

US-PAT-NO: 6169194
DOCUMENT-IDENTIFIER: US 6169194 B1

TITLE: High surface density covalent immobilization of oligonucleotide monolayers using a 1-(thiotrifluoroacetato)-11-(trichlorososilyl)-undecane linker

DATE-ISSUED: January 2, 2001

US-CL-CURRENT: 556/429; 204/600, 435/6, 436/524, 436/525, 436/527, 436/532, 562/83

APPL-NO: 8/ 951448
DATE FILED: October 16, 1997

L23: Entry 46 of 94 File: USPT Jan 2, 2001

DOCUMENT-IDENTIFIER: US 6169194 B1
TITLE: High surface density covalent immobilization of oligonucleotide monolayers using a 1-(thiotrifluoroacetato)-11-(trichlorososilyl)-undecane linker

Brief Summary Paragraph Right (13):
Alternatively, the nucleic acid can be constructed with a thiol linker which can be used to directly complex to gold surfaces (Ito, et. al., Anal. Chim. Acta., 1996, 327, 29). It is desired to fashion assemblies similar to the long-chain self-assembled monolayers of alkanethiols which have been described in the literature (Van Ness et. al., Nucleic Acids Res., 1991, 19, 3345). The thiol-nucleic acid probably cannot produce a close-packed surface due to the large hydrophilic nucleic acid group, and therefore its stability is questionable.

Detailed Description Paragraph Right (6):
Elemental analysis was performed by Canadian Microanalytical Service Ltd. (Delta, B.C.). The silane was handled in an inert atmosphere during handling and analysis. All elements except oxygen were determined.

Current US Cross Reference Classification (1):
204/600

Current US Cross Reference Classification (2):
435/6

Current US Cross Reference Classification (3):
436/524

Current US Cross Reference Classification (4):
436/525

Current US Cross Reference Classification (5):
436/527

Current US Cross Reference Classification (6):
436/532

Other Reference Publication (1):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research, 1996, vol. 24, No. 15, 3031-3039.

Other Reference Publication (3):
Lee et al., "Electrophilic siloxane-based self-assembled monolayers for thiol-mediated anchoring of peptides and proteins", Langmuir 1993, 9, 3009-3014.

47. Document ID: US 6165335 A

L23: Entry 47 of 94 File: USPT Dec 26, 2000

US-PAT-NO: 6165335
DOCUMENT-IDENTIFIER: US 6165335 A

TITLE: Biosensor device and method

L23: Entry 47 of 94 File: USPT Dec 26, 2000

US-PAT-NO: 6165335
DOCUMENT-IDENTIFIER: US 6165335 A

TITLE: Biosensor device and method

DATE-ISSUED: December 26, 2000

US-CL-CURRENT: 204/403.01; 204/403.06, 436/164, 436/908

APPL-NO: 8/ 845660
DATE FILED: April 24, 1997

PARENT-CASE:

BIOSENSOR DEVICE AND METHOD
This application claims the priority of U.S. Provisional Application No. 60/016,196 filed Apr. 25, 1996, and U.S. Provisional Application No. 60/016,385, filed Apr. 25, 1996, which are incorporated herein by reference.

L23: Entry 47 of 94 File: USPT Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165335 A
TITLE: Biosensor device and method

Brief Summary Paragraph Right (8):
Biosensors have a number of potential advantages over binding assay systems having separate reaction substrates and reader devices. One important advantage is the ability to manufacture small-scale, but highly reproducible, biosensor units using microchip manufacturing methods, as described, for example, in U.S. Pat. Nos. 5,200,051 and 5,212,050.

Brief Summary Paragraph Right (10):
A key element in the manufacture of biosensors, particularly multi-assay biosensors, is the placement of analyte-specific binding molecules or enzymes at desired locations on a biosensor surface. Ideally, it would be desirable to construct a universal biosensor surface under rigorous microchip manufacturing conditions, but allow a variety of different surface-region formats to be achieved under less restrictive manufacturing conditions, which at one extreme would allow an end user to tailor the universal chip to a unique multi-analyte format.

Detailed Description Paragraph Right (22):
Where the heterodimer is embedded in a hydrocarbon-chain monolayer, as described below, the spacer anchoring the HSP1 peptide to the biosensor surface may be a hydrocarbon chain, such as spacer chain 52 anchoring HSP1 to biosensor surface 50 in FIG. 4B. The chain is preferably a fractional length of the chains making up the bilayer, such that the distal ends of the heterodimer peptides in the assembled monolayer are at or near the exposed surface of the monolayer. Thus, for example, if the monolayer is made up of 18-carbon chains, the spacer is preferably 2-10 carbons in length, depending on the length of the assembled heterodimer.

Detailed Description Paragraph Right (69):
From the foregoing, it can be seen how various objects and advantages of the invention are met. The biosensor surface of the invention can be formed under controlled manufacturing conditions consistent with microchip scale and photomask processes, to produce highly uniform and/or miniaturized and/or high-density array sensor devices with attached HSP1 peptides.

Current US Original Classification (1):
204/403.01

Current US Cross Reference Classification (1):
204/403.06

Current US Cross Reference Classification (2):
436/164

Current US Cross Reference Classification (3):
436/908

48. Document ID: US 6159742 A

L23: Entry 48 of 94 File: USPT Dec 12, 2000

US-PAT-NO: 6159742
DOCUMENT-IDENTIFIER: US 6159742 A

TITLE: Nanometer-scale microscopy probes

L23: Entry 48 of 94 File: USPT Dec 12, 2000

US-PAT-NO: 6159742
DOCUMENT-IDENTIFIER: US 6159742 A

TITLE: Nanometer-scale microscopy probes

DATE-ISSUED: December 12, 2000

US-CL-CURRENT: 436/164; 422/55, 422/57, 436/171, 436/524, 436/526, 436/528, 436/535

APPL-NO: 9/ 326100
DATE FILED: June 4, 1999

PARENT-CASE:

CROSS REFERENCE
This application claims priority from U.S. Ser. No. 60/122,051 filed Jun. 5, 1998 under 35 USC 119(e)(1).

L23: Entry 48 of 94 File: USPT Dec 12, 2000

DOCUMENT-IDENTIFIER: US 6159742 A
TITLE: Nanometer-scale microscopy probes

Detailed Description Paragraph Right (12):
Once attached to the cantilever, the carbon-based nanotubes are shortened to a length between about 1 nm and 30 microns by applying, in an oxygen environment, a bias of about 1 to 50 Volts between the functionalized tip and a conductive surface, for example, a metal surface of sputtered Nb. The metal surface is, typically, placed about

10 to 50 nm away from the tip. Without being bound to any particular theory, it is believed that the applied voltage creates a momentary nanoscale arc that shortens the carbon-based nanotube.

Detailed Description Paragraph Right (19):
FIG. 2 shows a plot of force titrations between pH 2 and 9. The titrations were performed on hydroxyl-terminated self-assembled monolayers substrates (11-thioundecanol on gold-coated mica) with each functionalized MWNT tip. The functionalized groups on the MWNT tips are carboxyl, benzyl, and ethylamino.

Detailed Description Paragraph Right (24):
The use of functionalized MWNT for chemically-sensitive imaging has been investigated using patterned self-assembled monolayer substrates. Specifically, intermittent contact or tapping mode images were recorded in ethanol solution with carboxyl-terminated MWNT tips on substrates patterned with squares that terminate in CH.sub.3 groups and surrounded by COOH-- terminated regions. The patterned sample was prepared by microcontact printing and consisted of 10 .mu.m squares of a methyl-terminated (hexadecanethiol) self-assembled monolayer region surrounded by a carboxylic acid-terminated (16-mercaptohexadecanoic acid) self-assembled monolayer background on gold. Tapping mode images recorded with a carboxyl terminated MWNT exhibit a difference in phase between the two sample areas, although there is no difference in height: the tip-COOH/sample-COOH regions exhibit a phase lag relative to the tip-COOH/sample-CH.sub.3 regions. Phase lag differences can be quantitatively related to differences in the adhesion forces, and thus can be interpreted in terms of a map of the chemical functionality. See for example, Noy et al., Langmuir, 14, 1508, (1998). By using this technique, an image of the patterned sample can be created. The contrast in the image would correspond to phase variations between the different chemical regions of the sample. Images and force curves were acquired with a Nanoscope III (Digital Instruments, Inc.). Imaging parameters were optimized for individual tips; typical ranges for the FESP nanotube tips were (i) resonant frequencies, 28-33 kHz; (ii) free RMS oscillation amplitude, 30-90 nm, (iii) setpoint, 1-3 V, and (iv) scan rate, 0.5-1.2 Hz.

Detailed Description Paragraph Right (25):
The recorded adhesion force between the carboxyl-terminated nanotube tip and the COOH-terminated SAM is greater than the CH.sub.3 -terminated region. The greater adhesion is due to the hydrophilic-hydrophilic interaction of the MWNT functionalized tip and SAM. The hydrophilic-hydrophobic interaction of the MWNT functionalized tip and the self-assembled monolayer has a smaller adhesion. These results are consistent with chemically sensitive imaging.

Current US Original Classification (1):
436/164

Current US Cross Reference Classification (1):
422/55

Current US Cross Reference Classification (2):
422/57

Current US Cross Reference Classification (3):
436/171

Current US Cross Reference Classification (4):
436/524

Current US Cross Reference Classification (5):
436/526

Current US Cross Reference Classification (6):
436/528

Current US Cross Reference Classification (7):
436/535

49. Document ID: US 6159695 A

L23: Entry 49 of 94 File: USPT Dec 12, 2000

US-PAT-NO: 6159695
DOCUMENT-IDENTIFIER: US 6159695 A

TITLE: High surface density covalent immobilization of oligonucleotide monolayers

L23: Entry 49 of 94 File: USPT Dec 12, 2000

US-PAT-NO: 6159695
DOCUMENT-IDENTIFIER: US 6159695 A

TITLE: High surface density covalent immobilization of oligonucleotide monolayers

DATE-ISSUED: December 12, 2000

US-CL-CURRENT: 435/6; 427/299, 435/91.2

APPL-NO: 9/ 301287
DATE FILED: April 28, 1999

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS
This application is a continuation-in-part of U.S. patent application Ser. No. 08/954,448 filed Oct. 16, 1997, the entire disclosure of which is incorporated herein by reference.

L23: Entry 49 of 94 File: USPT Dec 12, 2000

DOCUMENT-IDENTIFIER: US 6159695 A
TITLE: High surface density covalent immobilization of oligonucleotide monolayers

Brief Summary Paragraph Right (13):
Alternatively, the nucleic acid can be constructed with a thiol linker which can be used to directly complex to gold surfaces (Ito, et. al., Anal. Chim. Acta., 1996, 327, 29). It is desirable to fashion assemblies similar to the long-chain self-assembled monolayers of alkanethiols which have been described in the literature (Van Ness et. al., Nucleic Acids Res., 1991, 19, 3345). The thiol-nucleic acid probably cannot produce a close-packed surface due to the large hydrophilic nucleic acid group, and therefore its stability is questionable.

Detailed Description Paragraph Right (31):
Elemental analysis was performed by Canadian Microanalytical Service Ltd. (Delta, B.C.). The silane was handled in an inert atmosphere during handling and analysis. All elements except oxygen were determined.

Current US Original Classification (1):
435/6

Current US Cross Reference Classification (2):
435/91.2

Other Reference Publication (2):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research, 1996, vol. 24, No. 15, 3031-3039.

50. Document ID: US 6149868 A

L23: Entry 50 of 94 File: USPT Nov 21, 2000

US-PAT-NO: 6149868
DOCUMENT-IDENTIFIER: US 6149868 A

TITLE: Surface enhanced raman scattering from metal nanoparticle-analyte-noble metal substrate sandwiches

L23: Entry 50 of 94 File: USPT Nov 21, 2000

US-PAT-NO: 6149868
DOCUMENT-IDENTIFIER: US 6149868 A

TITLE: Surface enhanced raman scattering from metal nanoparticle-analyte-noble metal substrate sandwiches

DATE-ISSUED: November 21, 2000

US-CL-CURRENT: 422/82.05; 356/301, 436/164

APPL-NO: 9/ 181291
DATE FILED: October 28, 1998

PARENT-CASE:

This application claims the benefit of U.S. Provisional Application Ser. No. 60/063,688, filed Oct. 28, 1997.

L23: Entry 50 of 94 File: USPT Nov 21, 2000

DOCUMENT-IDENTIFIER: US 6149868 A
TITLE: Surface enhanced raman scattering from metal nanoparticle-analyte-noble metal substrate sandwiches

Brief Summary Paragraph Right (3):
The literature teaches many approaches for creation, fabrication, or assembly of structures with the requisite nanoscale roughness. These include evaporated metal films, aggregated colloidal metal sols, electrochemically-roughened macroscopic electrodes, and a host of others. In all these approaches, the substance being studied by SERS is placed in direct or close contact with the surface.

Detailed Description Paragraph Right (58):
A final example concerns the use of macroscopic SERS substrates. FIG. 40 shows SERS data for sandwiches comprising Cc:Au complexes covalently bound (using carbodiimide coupling) to roughened Ag electrodes coated with 2-mercaptoethylamine. The change in SERS intensity as a function of electrochemical potential indicates close proximity of the Cc:Au complex to the electrode surface. These data also show that derivatization of the SERS substrate (here with a self-assembled monolayer of 2-mercaptoelthylamine) in no way inhibits either sandwich formation or spectral acquisition.

Detailed Description Paragraph Right (59):
Note that while the examples above describe sandwiches made with colloidal Au nanoparticles of various sizes between 12-60 nm, of Ag-clad Au nanoparticles, and of Ag nanoparticles, this is in no way limiting: the nanoparticle component of the sandwich can comprise particles of virtually any size smaller than visible wavelengths, any of several additional metals (Al, Cr, Cu, etc.), alloys of two or more metals, and inhomogeneous mixtures of two or more metals. Likewise, while the examples described herein have the analyte in direct contact with metal nanoparticle surfaces, a variety of surface-functionalized nanoparticles can be used. Such functionalization can take the form of a coating or thin film of any SERS-active or non-SERS active metal, a polymer or biopolymer, or mixtures thereof, a self-assembled monolayer of organothiols, organoisocyanides, and the like, metal oxides, or other nanoparticles. Such film can be

continuous or discontinuous, and of any thickness, as long as there is still an increased electromagnetic field at coating/surrounding interface.

Detailed Description Paragraph Right (60):
By the same token, while examples of the SERS substrate component of the sandwich consisted of aggregated Ag and Au sols and a macroscopic roughened Ag electrode, any previously described nanostructure that supports SERS can be used. Likewise, all the coatings described above with reference to the nanoparticle are equally viable for the SERS substrate, and not merely the organothiol self-assembled monolayer actually illustrated.

Current US Original Classification (1):
422/82.05

Current US Cross Reference Classification (2):
436/164

CLAIMS:

10. The invention as defined in claim 8 wherein the film is a self-assembled monolayer.

22. The invention as defined in claim 20 wherein the film is a self-assembled monolayer.

WEST

Generate Collection | Print

Search Results - Record(s) 51 through 94 of 94 returned.

51. Document ID: US 6143293 A

L24: Entry 51 of 94 File: USPT Nov 7, 2000

US-PAT-NO: 6143293
DOCUMENT-IDENTIFIER: US 6143293 A

TITLE: Assembled scaffolds for three dimensional cell culturing and tissue generation
DARE: Invalid display element.

L24: Entry 51 of 94 File: USPT Nov 7, 2000

DOCUMENT-IDENTIFIER: US 6143293 A
TITLE: Assembled scaffolds for three dimensional cell culturing and tissue generation

Brief Summary Paragraph Right (26):
According to the present invention, a three-dimensional scaffold is achieved by using mechanical fasteners, such as screws, sutures, and microbarbs in order to assemble layers and/or sections of scaffold material. In a preferred embodiment, cells have already been incorporated into each subsection of the scaffold prior to assembly.

Brief Summary Paragraph Right (28):
To help address the challenge of manufacturing heterogeneous scaffolds, the present invention provides a method to build up scaffold constructs by mechanical assembly of individual layer or volume elements. These individual elements can be prefabricated using existing scaffold manufacturing processes such as solvent casting, shaping sections with machining, 3D printing, or molded collagen/cell constructs. These sections can then be mechanically mated using biodegradable or non-biodegradable barbs, pins, screws, clamps, staples, wires, string, or sutures. With this mechanical assembly approach, each prefabricated section can first be seeded with cells before assembly, and different scaffold materials, scaffold microstructure, and different cells can be placed in different sections of the scaffold. In addition, surface features on each scaffold subsection, which are readily fabricated, become part of the internal microstructure (e.g., molded surface channels become conduits for cell infusion, or for blood flow to stimulate angiogenesis). Furthermore, prefabricated vessel constructs can be embedded and assembled into the scaffold as it is being built up. The proposed methodology is based, in part, on the solid freeform fabrication (SFF) manufacturing paradigm, described herein.

Drawing Description Paragraph Right (14):
FIG. 13 is a schematic representation of multiple scaffold layers assembled with screws and nuts according to the present invention.

Drawing Description Paragraph Right (15):
FIG. 14 is a schematic representation of assembling multiple layers of scaffold with miniature self-tapping screws according to the present invention.

Drawing Description Paragraph Right (16):
FIG. 15 is a schematic representation of multiple layers of scaffold being assembled with sutures according to the present invention.

Drawing Description Paragraph Right (17):
FIG. 16 is a schematic representation of multiple scaffold layers being assembled with pins according to the present invention.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

52. Document ID: US 6143247 A

L24: Entry 52 of 94 File: USPT Nov 7, 2000

US-PAT-NO: 6143247
DOCUMENT-IDENTIFIER: US 6143247 A

TITLE: Affinity binding-based system for detecting particulates in a fluid
DARE: Invalid display element.

L24: Entry 52 of 94 File: USPT Nov 7, 2000

DOCUMENT-IDENTIFIER: US 6143247 A
TITLE: Affinity binding-based system for detecting particulates in a fluid

Detailed Description Paragraph Right (27):
In embodiments of the inventive platforms wherein the reflective metal layer is gold, the surface can be treated with omega-substituted alkanethiol compounds of general formula HS--(CH.sub.2).sub.n -R (where n is an integer from 1 to about 50, and R is an alkyl, alkenyl, alkynyl, aryl or alkaryl group, or substituted derivatives thereof), to form self-assembled monolayers (SAM). SAMs formed from poly(ethylene glycol) terminated alkane thiols (e.g., R=(CH.sub.2 CH.sub.2 O).sub.m CH.sub.3) resist protein adhesion (see Prime et al., 1993, J. Amer. Chem. Soc. 115: 10714-10721) and have been used to block cell adhesion (see Singhvi et al., 1994, Science 264: 696-698). Gold surfaces have been coated with SAMs of hexadecanethiol (n=15, R.dbd.--CH.sub.3) to which laminin was adsorbed to provide a substrate suitable for cell attachment and growth (Singhvi et al., ibid.).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

53. Document ID: US 6140045 A

L24: Entry 53 of 94 File: USPT Oct 31, 2000

US-PAT-NO: 6140045
DOCUMENT-IDENTIFIER: US 6140045 A

TITLE: Multi-array, multi-specific electrochemiluminescence testing
DARE: Invalid display element.

L24: Entry 53 of 94 File: USPT Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6140045 A
TITLE: Multi-array, multi-specific electrochemiluminescence testing

Drawing Description Paragraph Right (15):
FIG. 11 illustrates the side view of a support having a metallic layer thereon to

provide a single electrode and binding surface assembly in the form of a cassette. An array of self-assembled monolayers ("SAMs") is patterned on the metallic layer.

Drawing Description Paragraph Right (17):
FIG. 13 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self assembled monolayers or SAMs is patterned on the metallic layer and the growth of a conducting polymer and/or fiber from the ECL label so as to extend the potential field around the ECL label of the sample to increase the efficiency of the ECL reaction, is illustrated.

Detailed Description Paragraph Right (3):
on a surface of a first support 10 and a plurality of electrode/counterelectrode pairs 16 are present on a surface of second support 12. The binding domains and electrode/counterelectrode pairs are aligned so that each of the plurality of electrode/counterelectrode pairs 16 is placed adjacent to a different one of the plurality of binding domains 14 when the first and second supports 10, 12 are brought together. First support 10 underlaying binding domains 14 is preferably a PMAMS with a gold film surface and transparent binding domains. Second support 12 is preferably a transparent flat plastic sheet having transparent electrode/counterelectrode pairs 16 thereon. Binding domains 14 are preferably prepared by micro stamping an organic self assembled monolayer (composed of individual monomers) pattern on the support surface, where the monomer has a biotin or linking moiety. Avidin or steptavidin is then bound to the exposed biotin (see e.g., U.S. Pat. No. 5,093,268). Binding reagents are then applied by applying a discrete amount of a suitable biotin-labeled binding reagent such as biotin labeled antibody, which is able to selectively bind to the analyte of interest, to the locations on the support surface where the monolayer had been stamped. FIG. 1A illustrates a system comprising a cassette (FIG. 1) contained in a housing (11).

Detailed Description Paragraph Right (24):
To better understand the invention, a more detailed description of the preparation of binding domains on a support is provided. A patterned array of binding domains on a surface that are specific for a plurality of analytes is referred to herein as a patterned, multi-array multi-specific surface or PMAMS. PMAMS are prepared on a support, for example, by patterning of self-assembled monolayers ("SAMs") (Ferguson et al, 1993, Macromolecules 26(22):5870-5875; Prime et al., 1991, Science 252:1164-1167; Laibinis et al., 1989, Science 245:845-847; Kumar et al., 1984, Langmuir 10(5):1498-1511; Bain et al., 1989, Angew. Chem. 101:522-528). Surface patterning methods also include the use of physical etching (e.g., micromachining) (Abbott et al., 1992, Science 257:1380-1382; Abbott, 1994, Chem. Mater. 6(5):596-602), microlithography (Laibinis et al., 1989, Science 245:845-847), attachment of chemical groups to the surface through the use of photoactivatable chemistries (Sundberg et al., 1995, J. Am. Chem. Soc. 117(49):12050-12057), and micro-stamping techniques (Kumar et al., 1994, Langmuir 10(5):1498-1511; Kumar et al., 1993, Appl. Phys. Lett. 63(14):2002-2004). Other surface patterning methods include procedures for the spatially controlled dispensing of fluids or particles (e.g., micropen deposition (e.g., using a microfluidic guide to deliver onto a surface using X-Y translation)), microcapillary filling (Kim et al., 1995, Nature 376:581), Ink-Jet technology, or syringe dispensers. Combinations of these techniques may be used to provide complex surface patterns. In FIG. 5A, a support 600 is shown with shape independent binding domains that are represented, simply for illustration purposes, as geometric shapes 602 to indicate that different binding specificities may be present on a single support. Surface 604 between binding domains may be alternatively hydrophobic or hydrophilic to confine deposition of binding reagent to form binding domains. Binding domains and/or the surface(s) between binding domains may be alternatively prone and resistant to nonspecific binding, and/or they may be prone and resistant to the attachment of binding reagents via covalent or non-covalent interactions. In the case where non-specific binding through hydrophobic interactions is not the desired method for attachment of binding chemistries to the surface, detergent may be added to prevent incidental non-specific binding from occurring.

Detailed Description Paragraph Right (35):
PMAMS can be generated from different types of surface binding groups. Self-assembling monolayers that can be used to form a monolayer on a surface to which they bind, include but are not limited to alkane thiols (which bind gold and other metals), alkyltrichlorosilane (e.g., which bind silicone/silicone dioxide), alkane carboxylic acids (e.g., which bind aluminum oxides) as well as combinations thereof. The monolayer may be formed first and then linking chemistry used to attach binding reagents.

Derivatization after self-assembly produces a more perfect two-dimensional crystalline packing of the monolayer on a support surface with fewer pin holes or defects. The monolayer can be derivatized with the binding reagents before or after self-assembly. Regular defects in the monolayer may be desirable, and can be obtained by derivatization prior to self-assembly of the monolayer or the support surface. If the derivatized group (e.g., exposed binding group) on the binding reagent is sterically large, it may create a close-packed surface at the exposed end, but with regular gaps at the metal surface. This is useful for allowing charge to flow through these regular gaps to the ECL labeled moieties bound to the portion contacting the sample solution.

Detailed Description Paragraph Right (273):
In a particular example of this aspect of the invention, binding domains, each of which have incorporated a different enzyme that utilizes as a substrate a sequential intermediate in a chemical reaction are situated on a PMAMS surface, such that the product of a given enzymatic reaction, which is the reactant for a subsequent enzyme, flows to the next enzyme in the reaction pathway. The invention also provides for bulk immobilization of enzymes on self-assembling monolayers, e.g., for industrial application, using methods as described above.

Other Reference Publication (7):
Abbott and Whitesides, 1994, Potential-Dependent Wetting of Aqueous Solutions on Self-Assembled Monolayers Formed from 15-(ferrocenylcarbonyl) pentadecanethiol on Gold, Langmuir 10: 1493-1497.

Other Reference Publication (11):
Bain and Whitesides, 1989, "Modeling Organic Surfaces with Self-Assembled Monolayers", Angew. Chem. 101:522-528.

Other Reference Publication (16):
DiMillia et al., 1994, "Wetting and Protein Adsorption of Self-Assembled (sic) Monolayers of Alkanethiolates Supported on Transparent Films of Gold," Journal of the American Chemical Society 116:2225-2226.

Other Reference Publication (38):
Pale-Grosdemange et al., 1991, "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo (ethylene Glycol) of Structure HS (CH2)11(OCH2CH2)m OH on Gold" Journal of the American Chemical Society 113 12-20.

Other Reference Publication (41):
Prime and Whitesides, 1993, "Adsorption of Proteins Onto Surfaces Containing End-Attached Oligo (ethylene oxide): A Model System Using Self-Assembled Monolayers" J. Amer. Chem. Soc. 115: 10714-721.

Other Reference Publication (42):
Prime and Whitesides, 1991, "Self-Assembled Organic Monolayers; Model Systems for Studying Adsorption of Proteins at Surfaces", Science 252: 1164-1167.

Other Reference Publication (51):
Wilber, et al., 1995, "Scanning Force Microscopies Can Image Patterned Self-Assembled Monolayers", Langmuir 11:825-831.

CLAIMS:

4. The method of claim 3 wherein said surface comprises a self-assembling monolayer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

54. Document ID: US 6139831 A

L24: Entry 54 of 94 File: USPT Oct 31, 2000

US-PAT-NO: 6139831
DOCUMENT-IDENTIFIER: US 6139831 A

TITLE: Apparatus and method for immobilizing molecules onto a substrate
DARE: Invalid display element.

L24: Entry 54 of 94 File: USPT Oct 31, 2000

DOCUMENT-IDENTIFIER: US 6139831 A
TITLE: Apparatus and method for immobilizing molecules onto a substrate

Brief Summary Paragraph Right (6):
One method of producing such chips borrows substantially from photolithographic microfabrication techniques developed and optimized by the computer microprocessor industry, which permit the economic production of large batches of chips using photographic templates. More specifically, current lithographic approaches for immobilizing molecules, particularly biomolecules onto a substrate, use chemical methods to specifically treat substrates with photoresist and then using photomasking, a light beam or an electron beam to define the pattern of immobilization of the molecule on the substrate. Examples of the use of this technique include microlithography on self-assembled monolayers and lipids, microcontact printing, microfluid networks and light directed combinatorial synthesis [Prime, K. L., and Whitesides, G. M. Science 252:1164 (1991); Dulcey, C. S. et al., Science 252:551 (1991); Berggren, K. K., et al., Science 269:1255 (1995); Jackman, R. J.,et al., Science 269:664 (1995); Healey, B. G., et al., Science 269:1078 (1995); Delamarche, E., et al., Science 276:779 (1997); Groves, J. T., et al., Science 275:651 (1997); and Burke, D. T., et al., Genome Research 7:189 (1997), all of which are hereby incorporated by reference in their entireties].

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw. Desc | Image

55. Document ID: US 6136269 A

L24: Entry 55 of 94 File: USPT Oct 24, 2000

US-PAT-NO: 6136269
DOCUMENT-IDENTIFIER: US 6136269 A

TITLE: Combinatorial kit for polymer synthesis
DARE: Invalid display element.

L24: Entry 55 of 94 File: USPT Oct 24, 2000

DOCUMENT-IDENTIFIER: US 6136269 A
TITLE: Combinatorial kit for polymer synthesis

Detailed Description Paragraph Right (81):
Methods for controlling chemical composition and therefore the local surface free energy of a substrate surface include a variety of techniques apparent to those skilled in the art. Chemical vapor deposition and other techniques applied in the fabrication of integrated circuits can be applied to deposit highly uniform layers on selected regions of a surface. As a specific example, the wettability of a silicon wafer surface has been manipulated on the micrometer scale through a combination of self-assembled monolayer depositions and micromachining. See Abbott et al., "Manipulation of the Wettability of Surfaces on the 0.1 to 1 Micrometer Scale Through Micromachining and Molecular Self-Assembly" Science, 257 (Sep. 4, 1992) which is incorporated herein by

reference for all purposes.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 56. Document ID: US 6132648 A

L24: Entry 56 of 94 File: USPT Oct 17, 2000

US-PAT-NO: 6132648
DOCUMENT-IDENTIFIER: US 6132648 A

TITLE: Devices and methods for generating electrogenerated chemiluminescence
DARE: Invalid display element.

L24: Entry 56 of 94 File: USPT Oct 17, 2000

DOCUMENT-IDENTIFIER: US 6132648 A
TITLE: Devices and methods for generating electrogenerated chemiluminescence

Detailed Description Paragraph Right (5):
This type of electrode is particularly suited for use with an aqueous electrolyte, which will tend to repel the hydrophobic tail portion 40 of the molecules 38 towards the surface of the electrode 34. Having the molecules of the coated layer assemble in an organized fashion as shown allows dense packing of the ECL molecules onto the electrode surface, thereby providing the ability for intense ECL emission in use.

Detailed Description Paragraph Right (10):
By providing an excitable monolayer assembly on conductive substrates, these ECL devices can be applied to studies of electron transfer and energy transfer processes at electrified interfaces, for example, the quenching of excited states with various electrode materials and under controlled potential. ECL has been used as a highly sensitive analytical method; the monolayer approach provided by various embodiments of this invention may provide even higher sensitivity, with a smaller amount of luminescors concentrated on an electrode surface.

Detailed Description Paragraph Right (45):
The emission from (III) on gold was intense enough to be dispersed into a spectrum as shown in FIG. 11. the emission peak of 650 nm as compared to 680 nm in Example 1 seems to suggest that the interaction between the chemisorbed species may not have been as ardent as in the mechanically assembled monolayers.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☒ 57. Document ID: US 6130098 A

L24: Entry 57 of 94 File: USPT Oct 10, 2000

US-PAT-NO: 6130098
DOCUMENT-IDENTIFIER: US 6130098 A

TITLE: Moving microdroplets
DARE: Invalid display element.

L24: Entry 57 of 94 File: USPT Oct 10, 2000

DOCUMENT-IDENTIFIER: US 6130098 A
TITLE: Moving microdroplets

Detailed Description Paragraph Right (10):
The present invention contemplates methods, compositions and devices for the creation of microdroplets of discrete (i.e. controlled and predetermined) size. The present invention contemplates the use of selective hydrophobic coatings to develop a liquid-sample injection and motion system that does not require the use of valves. In one embodiment, the present invention contemplates a method of lift-off to pattern hydrophobic and hydrophilic regions on glass, quartz and silicon substrates, involving i) the deposition of a hydrophobic reagent (such as a self-assembled monolayer film of OTS) on a silicon oxide surface pattered by a metal layer and ii) subsequent removal of the metal to give hydrophobic patterns. Other substrates such as plastics can also be used after depositing a think film of silicon oxide or spin-on-glass.

Detailed Description Paragraph Right (52):
A 0.1 .mu.m layer of Chromium metal is electronbeam deposited on the processed water. Photoresist PR 1827 is applied and spun at 2000 rpm for 30 seconds. The resist is patterned (SAM mask) and developed. The exposed Chromium metal is etched in Chromium etchant to expose the silicon oxide and the photoresist is then stripped off (STEP 5). The samples are then cleaned in Acetone, Isopropyl Alcohol and DI water for 10 minutes each, air dried and oven dried at 100.degree. C. for 5 minutes. The samples are then put in 1 wt % octadecyltrichlorosilane (OTS) solution in Toluene for 15-30 minutes. OTS deposits on the samples as a Self Assembled Monolayer (SAM) (STEP 6). The samples are then rinsed in Toluene, Isopropyl alcohol and DI water for 5 minutes each, and then oven dried (100.degree. C., 5 minutes). Next, they are put in Chromium etchant to remove the Chromium layer below. The SAM on the Chromium metal gets lifted off as a result of this. The samples were then rinsed in DI water and air dried, resulting in regions of intact hydrophobic regions on a hydrophilic oxide substrate (STEP 7). Heater elements and RTDs have also been fabricated on a quartz

58. Document ID: US 6130037 A

L24: Entry 58 of 94 File: USPT Oct 10, 2000

US-PAT-NO: 6130037
DOCUMENT-IDENTIFIER: US 6130037 A

TITLE: Biosensor device and method
DARE: Invalid display element.

L24: Entry 58 of 94 File: USPT Oct 10, 2000

DOCUMENT-IDENTIFIER: US 6130037 A
TITLE: Biosensor device and method

Detailed Description Paragraph Right (51):
Where the heterodimer is embedded in a hydrocarbonchain monolayer, as described below, the spacer anchoring the HSP1 peptide to the biosensor surface may be a hydrocarbon chain. The chain is preferably a fractional length of the chains making up the bilayer, such that the distal ends of the heterodimer peptides in the assembled monolayer are at or near the exposed surface of the monolayer. Thus, for example, if the monolayer is

made up of 18-carbon chains, the spacer is preferably 2-10 carbons in length, depending on the length of the assembled heterodimer.

59. Document ID: US 6129973 A

L24: Entry 59 of 94 File: USPT Oct 10, 2000

US-PAT-NO: 6129973
DOCUMENT-IDENTIFIER: US 6129973 A

TITLE: Microchannel laminated mass exchanger and method of making
DARE: Invalid display element.

L24: Entry 59 of 94 File: USPT Oct 10, 2000

DOCUMENT-IDENTIFIER: US 6129973 A
TITLE: Microchannel laminated mass exchanger and method of making

Detailed Description Paragraph Right (10):
The mass transfer medium may be a solid material, for example catalyst, absorbent material, adsorbent material, hydrophobic layer, hydrophilic layer, or combination thereof. The mass transfer medium may also be a porous or perforated material, wherein the term "porous material" refers to material through which diffusion occurs but bulk flow or "weeping" flow is prevented. When the pores or holes are of a size to permit bulk flow or weeping, the mass transfer medium is referred to herein as a perforated material. The porous or perforated material may also be a solid material or have a solid material thereon. A perforated material may be used for mixing two streams. An alternative form of mass transfer medium is a self assembling monolayer bonded to the surface of the outer thin sheet 118 within the margin 108, or bonded within the pores of a porous or perforated sheet wherein the self assembling monolayer further has one or

Detailed Description Paragraph Right (12):
For attachment of a self assembling monolayer, it may be necessary to coat a surface with an oxide material, for example silica, titania, or zirconia. Organic molecules useful as self assembling monolayers include silane, for example chlorosilane, alkoxysilane, and combinations thereof. Functional groups include but are not limited to mercaptan, mercaptan related compounds, amines, methyl, halogen, nitrile, pyradines, alkyls, polymers, and combinations thereof. For binding metals, tris(methoxy)mercaptopropysilane (TMMPS) has a thiol group with a high affinity for binding metals. Alternatively, therefore, using TMMPS on both ends of the organic molecule may permit attachment of the organic molecule directly to a metal outer thin sheet without a coating. By placing only hydroxyl functional groups on the organic molecule, water may be removed from a mixture to parts per trillion levels. For example a mixture of oil and water may have the water removed in this manner. This may be especially useful for removing tritiated water from oil. Inorganic materials may be attached via self assembling monolayers as described in W091/17286 published Nov. 14, 1991, PROCESS FOR DEPOSITING THIN FILM LAYERS ONTO SURFACES MODIFIED WITH ORGANIC FUNCTIONAL GROUPS AND PRODUCTS FORMED THEREBY, hereby incorporated by reference. Briefly, a polymeric surface is sulfonated then exposed to a solution of metal ionic species so that the metal ionic species deposits on the sulfonated surface as a solid layer.

CLAIMS:

17. The exchanger as recited in claim 16, wherein said solid material comprises catalyst, hydrophobic material, hydrophilic material, or self assembling monolayer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

60. Document ID: US 6117643 A

L24: Entry 60 of 94 File: USPT Sep 12, 2000

US-PAT-NO: 6117643
DOCUMENT-IDENTIFIER: US 6117643 A

TITLE: Bioluminescent bioreporter integrated circuit
DARE: Invalid display element.

L24: Entry 60 of 94 File: USPT Sep 12, 2000

DOCUMENT-IDENTIFIER: US 6117643 A
TITLE: Bioluminescent bioreporter integrated circuit

Detailed Description Paragraph Type 0 (176):
Mrksich and Whitesides, "Patterning self-assembled monolayers using microcontact printing: a new technology for biosensors," Trends Biotechnol., 13:228-235, 1995.

Other Reference Publication (22):
Mrksich and Whitesides, "Patterning self-assembled monolayers using microcontact printing: a new technology for biosensors," Trends Biotechnol., 13:228-235, 1995.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

61. Document ID: US 6107080 A

L24: Entry 61 of 94 File: USPT Aug 22, 2000

US-PAT-NO: 6107080
DOCUMENT-IDENTIFIER: US 6107080 A

TITLE: Biosensor device and method
DARE: Invalid display element.

L24: Entry 61 of 94 File: USPT Aug 22, 2000

DOCUMENT-IDENTIFIER: US 6107080 A
TITLE: Biosensor device and method

Detailed Description Paragraph Right (50):
Where the heterodimer is embedded in a hydrocarbon-chain monolayer, as described below, the spacer anchoring the HSP1 peptide to the biosensor surface may be a hydrocarbon chain. The chain is preferably a fractional length of the chains making up the bilayer, such that the distal ends of the heterodimer peptides in the assembled monolayer are at or near the exposed surface of the monolayer. Thus, for example, if the monolayer is

made up of 18-carbon chains, the spacer is preferably 2-10 carbons in length, depending on the length of the assembled heterodimer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 62. Document ID: US 6103479 A

L24: Entry 62 of 94 File: USPT Aug 15, 2000

US-PAT-NO: 6103479
DOCUMENT-IDENTIFIER: US 6103479 A

TITLE: Miniaturized cell array methods and apparatus for cell-based screening
DARE: Invalid display element.

L24: Entry 62 of 94 File: USPT Aug 15, 2000

DOCUMENT-IDENTIFIER: US 6103479 A
TITLE: Miniaturized cell array methods and apparatus for cell-based screening

Other Reference Publication (1):
Milan Mrksich and George M. Whitesides, "Using Self-Assembled Monolayers to Understand the Interactions of Man-Made Surfaces with Proteins and Cells," Annu. Rev. Biophys. Biomol. Struct., 1996, 25:55-78.

Other Reference Publication (4):
Gabriel P. Lopez, Mark W. Albers, Stuart L. Schreiber, Reed Carroll, Ernest Peralta and George M. Whitesides, Convenient Methods for Patterning the Adhesion of Mammalian Cells to Surfaces Using Self-Assembled Monolayers of Alkanethiolates on Gold, J. Am. Chem. Soc., 1993, 115, 5877-5878.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☐ 63. Document ID: US 6096273 A

L24: Entry 63 of 94 File: USPT Aug 1, 2000

US-PAT-NO: 6096273
DOCUMENT-IDENTIFIER: US 6096273 A

TITLE: Electrodes linked via conductive oligomers to nucleic acids
DARE: Invalid display element.

L24: Entry 63 of 94 File: USPT Aug 1, 2000

DOCUMENT-IDENTIFIER: US 6096273 A
TITLE: Electrodes linked via conductive oligomers to nucleic acids

Other Reference Publication (13):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of

11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (14):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta. 36(11/12):1799-1801 (1991).

Other Reference Publication (79):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, bp-bp-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces", J. Am. Chem. Soc. 117:9529-9534 (1995).

Other Reference Publication (85):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research 24(15):3031-3039 (1996).

Other Reference Publication (97):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers", J. Am. Chem. Soc. 112:4301-4306 (1990).

Other Reference Publication (109):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem. 68(3):490-497 (1996).

64. Document ID: US 6090933 A

L24: Entry 64 of 94 File: USPT Jul 18, 2000

US-PAT-NO: 6090933
DOCUMENT-IDENTIFIER: US 6090933 A

TITLE: Methods of attaching conductive oligomers to electrodes
DARE: Invalid display element.

L24: Entry 64 of 94 File: USPT Jul 18, 2000

DOCUMENT-IDENTIFIER: US 6090933 A
TITLE: Methods of attaching conductive oligomers to electrodes

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):

Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

65. Document ID: US 6090545 A

L24: Entry 65 of 94 File: USPT Jul 18, 2000

US-PAT-NO: 6090545
DOCUMENT-IDENTIFIER: US 6090545 A

TITLE: Multi-array, multi-specific electrochemiluminescence testing
DARE: Invalid display element.

L24: Entry 65 of 94 File: USPT Jul 18, 2000

DOCUMENT-IDENTIFIER: US 6090545 A
TITLE: Multi-array, multi-specific electrochemiluminescence testing

Drawing Description Paragraph Right (16):
FIG. 11 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self-assembled monolayers ("SAMs") is patterned on the metallic layer.

Drawing Description Paragraph Right (18):
FIG. 13 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self assembled monolayers or SAMs is patterned on the metallic layer and the growth of a conducting polymer and/or fiber from the ECL label so as to extend the potential field around the ECL label of the sample to increase the efficiency of the ECL reaction, is illustrated.

Detailed Description Paragraph Right (2):
In the embodiment of the invention shown in FIG. 1, a cassette comprises two supports 10, 12 wherein a plurality of binding domains 14 are present on a surface of a first support 10 and a plurality of electrode/counterelectrode pairs 16 are present on a surface of second support 12. The binding domains and electrode/counterelectrode pairs are aligned so that each of the plurality of electrode/counterelectrode pairs 16 is placed adjacent to a different one of the plurality of binding domains 14 when the first and second supports 10, 12 are brought together. First support 10 underlaying binding domains 14 is preferably a PMAMS with a gold film surface and transparent binding domains. Second support 12 is preferably a transparent flat plastic sheet having transparent electrode/counterelectrode pairs 16 thereon. Binding domains 14 are preferably prepared by micro stamping an organic self assembled monolayer (composed of individual monomers) pattern on the support surface, where the monomer has a biotin or linking moiety. Avidin or steptavidin is then bound to the exposed biotin (see e.g., U.S. Pat. No. 5,093,268). Binding reagents are then applied by applying a discrete amount of a suitable biotin-labeled binding reagent such as biotin labeled antibody, which is able to selectively bind to the analyte of interest, to the locations on the support surface where the monolayer had been stamped. FIG. 1A illustrates a system comprising a cassette (FIG. 1) contained in a housing (11).

Detailed Description Paragraph Right (23):
To better understand the invention, a more detailed description of the preparation of binding domains on a support is provided. A patterned array of binding domains on a surface that are specific for a plurality of analytes is referred to herein as a patterned, multi-array multi-specific surface or PMAMS. PMAMS are prepared on a support, for example, by patterning of self-assembled monolayers ("SAMs") (Ferguson et al, 1993, Macromolecules 26(22):5870-5875; Prime et al., 1991, Science 252:1164-1167; Laibinis et al., 1989, Science 245:845-847; Kumar et al., 1984, Langmuir 10(5):1498-1511; Bain et al., 1989, Angew. Chem. 101:522-528). Surface patterning methods also include the use of physical etching (e.g., micromachining) (Abbott et al., 1992, Science 257:1380-1382; Abbott, 1994, Chem. Mater. 6(5):596-602), microlithography (Laibinis et al., 1989, Science 245:845-847), attachment of chemical groups to the surface through the use of photoactivatable chemistries (Sundberg et al., 1995, J. Am. Chem. Soc. 117(49):12050-12057), and micro-stamping techniques (Kumar et al., 1994, Langmuir 10(5):1498-1511; Kumar et al., 1993, Appl. Phys. Lett. 63(14):2002-2004). Other surface patterning methods include procedures for the spatially controlled dispensing of fluids or particles (e.g., micropen deposition (e.g., using a microfluidic guide to deliver onto a surface using X-Y translation)), microcapillary filling (Kim et al., 1995, Nature 376:581), Ink-Jet technology, or syringe dispensers. Combinations of these techniques may be used to provide complex surface patterns. In FIG. 5A, a support 600 is shown with shape independent binding domains that are represented, simply for illustration purposes, as geometric shapes 602 to indicate that different binding specificities may be present on a single support. Surface 604 between binding domains may be alternatively hydrophobic or hydrophilic to confine deposition of binding reagent to form binding domains. Binding domains and/or the surface(s) between binding domains may be alternatively prone and resistant to nonspecific binding, and/or they may be prone and resistant to the attachment of binding reagents via covalent or non-covalent interactions. In the case where non-specific binding through hydrophobic interactions is not the desired method for attachment of binding chemistries to the surface, detergent may be added to prevent incidental non-specific binding from occurring.

Detailed Description Paragraph Right (33):
PMAMS can be generated from different types of surface binding groups. Self-assembling monolayers that can be used to form a monolayer on a surface to which they bind, include but are not limited to alkane thiols (which bind gold and other metals), alkyltrichlorosilane (e.g., which bind silicone/silicone dioxide), alkane carboxylic acids (e.g., which bind aluminum oxides) as well as combinations thereof. The monolayer may be formed first and then linking chemistry used to attach binding reagents. Derivatization after self-assembly produces a more perfect two-dimensional crystalline packing of the monolayer on a support surface with fewer pin holes or defects. The monolayer can be derivatized with the binding reagents before or after self-assembly. Regular defects in the monolayer may be desirable, and can be obtained by derivatization prior to self-assembly of the monolayer or the support surface. If the derivatized group (e.g., exposed binding group) on the binding reagent is sterically large, it may create a close-packed surface at the exposed end, but with regular gaps at the metal surface. This is useful for allowing charge to flow through these regular gaps to the ECL labeled moieties bound to the portion contacting the sample solution.

Detailed Description Paragraph Right (273):
In a particular example of this aspect of the invention, binding domains, each of which have incorporated a different enzyme that utilizes as a substrate a sequential intermediate in a chemical reaction are situated on a PMAMS surface, such that the product of a given enzymatic reaction, which is the reactant for a subsequent enzyme, flows to the next enzyme in the reaction pathway. The invention also provides for bulk immobilization of enzymes on self-assembling monolayers, e.g., for industrial application, using methods as described above.

Other Reference Publication (1):
Abbott and Whitesides, 1994, Potential-Dependent Wetting of Aqueous Solutions on Self-Assembled Monolayers Formed from 15-(ferrocenylcarbonyl) pentadecanethiol on Gold, Langmuir 10 1493-1497.

Other Reference Publication (5):
Bain and Whitesides, 1989, "Modeling Organic Surfaces with Self-Assembled Monolayers", Angew. Chem. 101:522-528.

Other Reference Publication (10):
DiMillia et al., 1994, "Wetting and Protein Adsorption of Self-Assembled (sic)

Monolayers of Alkanethiolates Supported on Transparent Films of Gold," Journal of the American Chemical Society 116 2225-2226.

Other Reference Publication (33):
Pale-Grosdemange et al., 1991, "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo (ethylene Glycol) of Structure HS (CH2)11(OCH2CH2)m OH on Gold" Journal of the American Chemical Society 113 12-20.

Other Reference Publication (36):
Prime and Whitesides, 1993, "Adsorption of Proteins Onto Surfaces Containing End-Attached Oligo (ethylene oxide): A Model System Using Self-Assembled Monolayers" J. Amer. Chem. Soc. 115: 10714-721.

Other Reference Publication (37):
Prime and Whitesides, 1991, "Self-Assembled Organic Monolayers; Model Systems for Studying Adsorption of Proteins at Surfaces", Science 252: 1164-1167.

Other Reference Publication (46):
Wilber, et al., 1995, "Scanning Force Microscopies Can Image Patterned Self-Assembled Monolayers", Langmuir 11825-831.

66. Document ID: US 6087100 A

L24: Entry 66 of 94 File: USPT Jul 11, 2000

US-PAT-NO: 6087100
DOCUMENT-IDENTIFIER: US 6087100 A

TITLE: Nucleic acid mediated electron transfer
DARE: Invalid display element.

L24: Entry 66 of 94 File: USPT Jul 11, 2000

DOCUMENT-IDENTIFIER: US 6087100 A
TITLE: Nucleic acid mediated electron transfer

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

67. Document ID: US 6073482 A

L24: Entry 67 of 94 File: USPT Jun 13, 2000

US-PAT-NO: 6073482
DOCUMENT-IDENTIFIER: US 6073482 A

TITLE: Fluid flow module
DARE: Invalid display element.

L24: Entry 67 of 94 File: USPT Jun 13, 2000

DOCUMENT-IDENTIFIER: US 6073482 A
TITLE: Fluid flow module

Brief Summary Paragraph Right (13):
In accordance with a preferred embodiment of the invention, the module, in its simplest form, is fabricated from a valve layer and a pair of channel bearing layers and these layers are formed from self-bondable polyimide sheets. The invention also provides a method for fabricating the module using self-bondable polyimide sheets wherein the channel bearing layers and the valve layer are assembled and directly interfacially bonded to is one another using heat and pressure as described in more detail herein. In accordance with the invention, in order to prevent the valve layer from bonding to the channel bearing layer in the valve region, a release agent is applied in this region. The release agent is preferably applied to the surface of the channel bearing layer adjacent the valve layer, but the release agent could be applied to the corresponding valve region of the valve layer instead of or in addition to applying the release agent to the

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

68. Document ID: US 6071699 A

L24: Entry 68 of 94 File: USPT Jun 6, 2000

US-PAT-NO: 6071699
DOCUMENT-IDENTIFIER: US 6071699 A

TITLE: Nucleic acid mediated electron transfer
DARE: Invalid display element.

L24: Entry 68 of 94 File: USPT Jun 6, 2000

DOCUMENT-IDENTIFIER: US 6071699 A
TITLE: Nucleic acid mediated electron transfer

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (74):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-107 -Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

69. Document ID: US 6066448 A

L24: Entry 69 of 94 File: USPT May 23, 2000

US-PAT-NO: 6066448
DOCUMENT-IDENTIFIER: US 6066448 A

TITLE: Multi-array, multi-specific electrochemiluminescence testing
DARE: Invalid display element.

L24: Entry 69 of 94 File: USPT May 23, 2000

DOCUMENT-IDENTIFIER: US 6066448 A
TITLE: Multi-array, multi-specific electrochemiluminescence testing

Drawing Description Paragraph Right (16):
FIG. 11 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self-assembled monolayers ("SAMs") is patterned on the metallic layer.

Drawing Description Paragraph Right (18):
FIG. 13 illustrates the side view of a support having a metallic layer thereon to provide a single electrode and binding surface assembly in the form of a cassette. An array of self assembled monolayers or SAMs is patterned on the metallic layer and the growth of a conducting polymer and/or fiber from the ECL label so as to extend the potential field around the ECL label of the sample to increase the efficiency of the

ECL reaction, is illustrated.

Detailed Description Paragraph Right (2):
In the embodiment of the invention shown in FIG. 1, a cassette comprises two supports 10, 12 wherein a plurality of binding domains 14 are present on a surface of a first support 10 and a plurality of electrode/counterelectrode pairs 16 are present on a surface of second support 12. The binding domains and electrode/counterelectrode pairs are aligned so that each of the plurality of electrode/counterelectrode pairs 16 is placed adjacent to a different one of the plurality of binding domains 14 when the first and second supports 10, 12 are brought together. First support 10 underlaying binding domains 14 is preferably a PMAMS with a gold film surface and transparent binding domains. Second support 12 is preferably a transparent flat plastic sheet having transparent electrode/counterelectrode pairs 16 thereon. Binding domains 14 are preferably prepared by micro stamping an organic self assembled monolayer (composed of individual monomers) pattern on the support surface, where the monomer has a biotin or linking moiety. Avidin or steptavidin is then bound to the exposed biotin (see e.g., U.S. Pat. No. 5,093,268). Binding reagents are then applied by applying a discrete amount of a suitable biotin-labeled binding reagent such as biotin labeled antibody, which is able to selectively bind to the analyte of interest, to the locations on the support surface where the monolayer had been stamped. FIG. 1A illustrates a system comprising a cassette (FIG. 1) contained in a housing (11).

Detailed Description Paragraph Right (23):
To better understand the invention, a more detailed description of the preparation of binding domains on a support is provided. A patterned array of binding domains on a surface that are specific for a plurality of analytes is referred to herein as a patterned, multi-array multi-specific surface or PMAMS. PMAMS are prepared on a support, for example, by patterning of self-assembled monolayers ("SAMs") (Ferguson et al, 1993, Macromolecules 26(22):5870-5875; Prime et al., 1991, Science 252:1164-1167; Laibinis et al., 1989, Science 245:845-847; Kumar et al., 1984, Langmuir 10(5):1498-1511; Bain et al., 1989, Angew. Chem. 101:522-528). Surface patterning methods also include the use of physical etching (e.g., micromachining) (Abbott et al., 1992, Science 257:1380-1382; Abbott, 1994, Chem. Mater. 6(5):596-602), microlithography (Laibinis et al., 1989, Science 245:845-847), attachment of chemical groups to the surface through the use of photoactivatable chemistries (Sundberg et al., 1995, J. Am. Chem. Soc. 117(49):12050-12057), and micro-stamping techniques (Kumar et al., 1994, Langmuir 10(5):1498-1511; Kumar et al., 1993, Appl. Phys. Lett. 63(14):2002-2004). Other surface patterning methods include procedures for the spatially controlled dispensing of fluids or particles (e.g., micropen deposition (e.g., using a microfluidic guide to deliver onto a surface using X-Y translation)), microcapillary filling (Kim et al., 1995, Nature 376:581), Ink-Jet technology, or syringe dispensers. Combinations of these techniques may be used to provide complex surface patterns. In FIG. 5A, a support 600 is shown with shape independent binding domains that are represented, simply for illustration purposes, as geometric shapes 602 to indicate that different binding specificities may be present on a single support. Surface 604 between binding domains may be alternatively hydrophobic or hydrophilic to confine deposition of binding reagent to form binding domains. Binding domains and/or the surface(s) between binding domains may be alternatively prone and resistant to nonspecific binding, and/or they may be prone and resistant to the attachment of binding reagents via covalent or non-covalent interactions. In the case where non-specific binding through hydrophobic interactions is not the desired method for attachment of binding chemistries to the surface, detergent may be added to prevent incidental non-specific binding from occurring.

Detailed Description Paragraph Right (33):
PMAMS can be generated from different types of surface binding groups. Self-assembling monolayers that can be used to form a monolayer on a surface to which they bind, include but are not limited to alkane thiols (which bind gold and other metals), alkyltrichlorosilane (e.g., which bind silicone/silicone dioxide), alkane carboxylic acids (e.g., which bind aluminum oxides) as well as combinations thereof. The monolayer may be formed first and then linking chemistry used to attach binding reagents. Derivatization after self-assembly produces a more perfect two-dimensional crystalline packing of the monolayer on a support surface with fewer pin holes or defects. The monolayer can be derivatized with the binding reagents before or after self-assembly. Regular defects in the monolayer may be desirable, and can be obtained by derivatization prior to self-assembly of the monolayer or the support surface. If the derivatized group (e.g., exposed binding group) on the binding reagent is sterically large, it may create a close-packed surface at the exposed end, but with regular gaps at the metal surface. This is useful for allowing charge to flow through these regular

gaps to the ECL labeled moieties bound to the portion contacting the sample solution.

Detailed Description Paragraph Right (274):
In a particular example of this aspect of the invention, binding domains, each of which have incorporated a different enzyme that utilizes as a substrate a sequential intermediate in a chemical reaction are situated on a PMAMS surface, such that the product of a given enzymatic reaction, which is the reactant for a subsequent enzyme, flows to the next enzyme in the reaction pathway. The invention also provides for bulk immobilization of enzymes on self-assembling monolayers, e.g., for industrial application, using methods as described above.

Other Reference Publication (6):
Abbott and Whitesides, 1994, Potential-Dependent Wetting of Aqueous Solutions on Self-Assembled Monolayers Formed from 15--(ferrocenylcarbonyl) pentadecanethiol on Gold, Langmuir 10: 1493-1497.

Other Reference Publication (10):
Basin and Whitesides, 1989, "Modeling Organic Surfaces with Self-Assembled Monolayers", Angew. Chem. 101: 522-528.

Other Reference Publication (27):
DiMillia et al., 1994, "Wetting and Protein Adsorption of Self-Assembled (sic) Monolayers of Alkanethiolates Supported on Transparent Films of Gold," Journal of The American Chemical Society 116: 2225-2226.

Other Reference Publication (38):
Pale-Grosdemange et al., 1991, "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo (ethylene Glycol) of Structure HS (CH2)11(OCH2CH2) m OH on Gold" Journal of the American Chemical Society 113: 12-20.

Other Reference Publication (41):
Prime and Whitesides, 1993, "Adsorption of Proteins onto Surfaces Containing End-Attached Oligo (ethylene oxide) : A Model System Using Self-Assembled Monolayers" J. Amer. Chem. Soc. 115: 10714-721.

Other Reference Publication (42):
Prime and Whitesides, 1991, "Self-Assembled Organic Monolayers; Model Systems for Studying Adsorptions of Proteins at Surfaces", Science 252: 1164-1167.

Other Reference Publication (51):
Wilber, et al., 1995, "Scanning Force Microscopies Can Image Patterned Self-Assembled Monolayers", Langmuir 11: 825-831.

CLAIMS:

57. The apparatus of claims 9, 21, 32, 33, 34, 35, 37, 38 or 39, wherein said binding domains comprise patterned, self-assembled monolayers.

58. The apparatus of claims 9, 21, 32, 33, 34, 35, 37, 38 or 39, wherein said binding domains comprise patterned, self-assembled monolayers and said patterned self-assembled monolayers comprise alkane thiol.

107. The kit of claim 28, wherein said support comprises:

(a) conducting polymers;

(b) conductive particles dispersed in a matrix;

(c) conductive fibers;

(d) a patterned self-assembled monolayer; or

(e) mixtures thereof.

108. The kit of claim 30, wherein said electrode comprises:

(a) conducting polymers;

(b) conductive particles dispersed in a matrix;

(c) conductive fibers;

(d) a patterned self-assembled monolayer; or

(e) mixtures thereof.

118. The kit as recited in claim 117, wherein said surface comprises a self-assembling monolayer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

70. Document ID: US 6040193 A

~~L24~~: Entry 70 of 94 File: USPT Mar 21, 2000

US-PAT-NO: 6040193
DOCUMENT-IDENTIFIER: US 6040193 A

TITLE: Combinatorial strategies for polymer synthesis
DARE: Invalid display element.

L24: Entry 70 of 94 File: USPT Mar 21, 2000

DOCUMENT-IDENTIFIER: US 6040193 A
TITLE: Combinatorial strategies for polymer synthesis

Detailed Description Paragraph Right (78):
Methods for controlling chemical composition and therefore the local surface free energy of a substrate surface include a variety of techniques apparent to those skilled in the art. Chemical vapor deposition and other techniques applied in the fabrication of integrated circuits can be applied to deposit highly uniform layers on selected regions of a surface. As a specific example, the wettability of a silicon wafer surface has been manipulated on the micrometer scale through a combination of self-assembled monolayer depositions and micromachining. See Abbott et al., "Manipulation of the Wettability of Surfaces on the 0.1 to 1 Micrometer Scale Through Micromachining and Molecular Self-Assembly" Science, 257 (Sept. 4, 1992) which is incorporated herein by reference for all purposes.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

71. Document ID: US 6036927 A

L24: Entry 71 of 94 File: USPT Mar 14, 2000

US-PAT-NO: 6036927
DOCUMENT-IDENTIFIER: US 6036927 A

TITLE: Micro-ceramic chemical plant having catalytic reaction chamber
DARE: Invalid display element.

L24: Entry 71 of 94 File: USPT Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6036927 A
TITLE: Micro-ceramic chemical plant having catalytic reaction chamber

Detailed Description Paragraph Right (11):
The permeable partition wall 36 is preferably made by dry pressing ceramic and its composite powders such as zirconia silicate, alumina silicate, zirconia, alumina, silicon carbide, silicon nitride and ceramic composites comprising zirconia-alumina at a pressure such that upon sintering the desired degree of porosity is maintained. It is very important that the pores need to of interconnecting variety. The permeable partition wall 36 can also be made alternatively by gel casting, tape casting and injection molding zirconia silicate or alumina silicate such that upon controlled sintering for each part or item different degrees of porosity are achieved. The permeable partition wall 36 permits controlled reaction between the chemicals in the fluids on either side of the permeable partition wall 36 to permit the mixing of such fluids during a reaction process. The ceramic powder is blended with polymeric fibers such as polyvinyl alcohol, polyethylene glycol or acrylic which upon sintering leaves behind interconnected micropores. The pore size or the diameter of the sacrificial organic fibers vary in a range from 0.1 to 10 .mu.m because the degree of porosity (density) is warranted by the amount of permeability required for a given chemical process. In other words, custom tailored permeability can be incorporated by controlling the compacting pressure, diameter of the polymer fibers and sintering temperature for a given ceramic composition. The preferred way of making the green permeable partition wall 36 containing sacrificial organic fibers such as polyvinyl alcohol, is to gel cast the ceramic mixture containing the organic binders and organic fibers in a mold and air drying the part to drive off the solvent. Upon compacting and subsequent firing the sacrificial organic fibers will produce a wall having a variable degree of porosity. The permeable partition wall 36, which is in the green state, is then incorporated in the unitary ceramic green body before all the layers are assembled and sintered to form the sintered unitary micro-ceramic chemical plant. It is instructive to note that a plurality of channels can be provided to handle more than two chemicals or alternatively the catalytic reaction chamber 34 can be made longer by configuring serpentine, complex, wavy, winding and angular meandering forms to allow for longer reaction time. An embedded ceramic heating element 38 is provided in walls defining the perimeter of the catalytic reaction chamber 34 to provide heat to the catalytic reaction chamber 34. The embedded heating element 38 can be made from ceramics such as MoSi.sub.2, TiB.sub.2, ZrB.sub.2, WO.sub.3 or high-temperature resistive metals or metallic alloys. The electrical leads 40 for the embedded heating element 38 are located at the side of the ceramic second layer 30 defining the perimeter of the catalytic reaction chamber 34, and is an integral part thereof. The thermocouple feedthrough 41 located close to the heating element and the thermocouple (not shown) can be inserted in the thermocouple feedthrough 41 for both monitor and control of temperature of the reaction chamber. This layer also contain catalytic reaction beds to facilitate catalytic reactions. The catalytic reaction beds are micro-porous ceramics embedded with catalysts.

72. Document ID: US 6025202 A

L24: Entry 72 of 94 File: USPT Feb 15, 2000

US-PAT-NO: 6025202
DOCUMENT-IDENTIFIER: US 6025202 A

TITLE: Self-assembled metal colloid monolayers and detection methods therewith
DARE: Invalid display element.

L24: Entry 72 of 94 File: USPT Feb 15, 2000

DOCUMENT-IDENTIFIER: US 6025202 A
TITLE: Self-assembled metal colloid monolayers and detection methods therewith

Detailed Description Paragraph Right (29):
The following materials were obtained from Aldrich: HAuCl.sub.4.3H.sub.2 O, AgNO.sub.3, trisodium citrate dihydrate, trans-1,2 bis(4-pyridyl)ethylene (BPE), and trimethoxy-propylsilane. The following organosilanes were obtained from Huls America, Inc., and used as received: (3-aminopropyl)trimethoxysilane (APTMS), (3-cyanopropyldimethyl)methoxysilane (CPDMMS), (3-mercaptopropylmethyl)dimethoxysilane (MPMDMS), and 3-cyanopropyltriethoxysilane (CPTES). Concentrated HCl, HNO.sub.3, and H.sub.2 SO.sub.4 were purchased from J. T. Baker Inc., and 30% H.sub.2 O.sub.2 was obtained from VWR. CH.sub.3 OH (spectrophotometric grade) was obtained from EM Science; all H.sub.2 O was 18 MW, distilled through a Barnstead Nanopure water purification system. Streptavidin, bovine serum albumin (BSA), and 3-(N-maleimidopropionyl)biocytin (MP-biocytin) were purchased from Sigma. BPE was recrystallized several times from a mixture of H.sub.2 O and CH.sub.3 OH; the other materials were used as received. Substrates were obtained as follows: glass and quartz microscope slides from Fisher Scientific and Technical Glass Products, respectively; SiO.sub.x -coated TEM grids from Ted Pella, Inc.; and self-assembled monolayers (SAMs) of HS(CH.sub.2).sub.18 CO.sub.2 H on Au foil from literature procedures [Bain, C. D.; Troughton, E. B.; Tao, Y.-T.; Evall, J.; Whitesides, G. M.; Nuzzo, R. G. J. Am. Chem. Soc. 1989, 111, 321-35].

Detailed Description Paragraph Right (96):
The most likely interferences in SERS are adsorption of inorganic anions (HO.sup.-, HCOO.sup.-, etc.) Their influence can be minimized by acidifcation; at pH 5, [HO-]=10.sup.-9. Thus a simple route to identify (and eliminate) undesired adsorbates is to acquire Raman spectra at several pH's. Halide anions are bound more tightly, but each have only one band in the Raman spectrum, so that their net effect is essentially limited to a reduction of available OPP binding sites. If this leads to significant problems, it can be overcome by introducing an element of molecular selectivity at the Au/Ag interface. The introduction of organothiol self-assembled monolayers (SAMs) onto SERS-active surfaces increases selectivity for the desired analytes, and that partition from solution into the SAM film can be quantitated. A similar strategy can be adopted with regard to the inventive method using HSCH.sub.2 CH.sub.2 OH or HSCH.sub.2 CH.sub.2 NH.sub.3.sup.+. Monolayers of the first molecule should preferentially hydrogen bond with the P=S or P=O functional group relative to H.sub.2 O, HO.sup.-, or halide. Note that direct analyte adsorption is not necessary for SERS: enhancement by the so-called electromagnetic effect--which accounts for 10.sup.4 of the 10.sup.6 overall enhancement--is still quite substantial 10 .ANG. from the surface.

73. Document ID: US 6013459 A

L24: Entry 73 of 94 File: USPT Jan 11, 2000

US-PAT-NO: 6013459
DOCUMENT-IDENTIFIER: US 6013459 A

TITLE: Detection of analytes using reorganization energy
DARE: Invalid display element.

L24: Entry 73 of 94 File: USPT Jan 11, 2000

DOCUMENT-IDENTIFIER: US 6013459 A

TITLE: Detection of analytes using reorganization energy

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (74):
Sata, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (79):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (86):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (90):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

74. Document ID: US 6013170 A

L24: Entry 74 of 94 File: USPT Jan 11, 2000

US-PAT-NO: 6013170
DOCUMENT-IDENTIFIER: US 6013170 A

TITLE: Detection of analytes using reorganization energy
DARE: Invalid display element.

L24: Entry 74 of 94 File: USPT Jan 11, 2000

DOCUMENT-IDENTIFIER: US 6013170 A
TITLE: Detection of analytes using reorganization energy

Other Reference Publication (15):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold " Electroactive Self-Assembled Monolayers, J. Am. Chem. Soc., 112:4301-4306 (1990).

Other Reference Publication (16):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (72):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (77):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem., 68(3):490-497 (1996).

Other Reference Publication (84):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (88):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

CLAIMS:

4. A composition according to claim 1 wherein said electrode further comprises a self-assembled monolayer.

11. An apparatus according to claim 8 wherein said electrode further comprises a self-assembled monolayer.

75. Document ID: US 5989835 A

L24: Entry 75 of 94 File: USPT Nov 23, 1999

US-PAT-NO: 5989835
DOCUMENT-IDENTIFIER: US 5989835 A

TITLE: System for cell-based screening
DARE: Invalid display element.

L24: Entry 75 of 94 File: USPT Nov 23, 1999

DOCUMENT-IDENTIFIER: US 5989835 A
TITLE: System for cell-based screening

Detailed Description Paragraph Type 0 (3):
3) C. S. Dulcey, J. H. Georger, M. S. Chen, S. McElvany, C. E. O'Ferrall, V. I. Benezra, and J. M. Calvert, "Photochemistry and Patterning of Self-Assembled Monolayer Films Containing Aromatic Hydrocarbon Functional Groups", Langmuir, 1996, 12, 1638.

Detailed Description Paragraph Type 0 (4):
4) W. J. Dressick, C. S. Dulcey, M. S. Chen, and J. M. Calvert "Photochemical Studies of (Aminoethylaminomethyl) phenethyltrimethoxysilane (PEDA) Self-Assembled Monolayer Films", Thin Solid Films, 1996, in press.

Detailed Description Paragraph Type 0 (6):
6) B. J. Spargo, M. A. Testoff, T. Nielson, D. A. Stenger, J. J. Hickman, and A. S. Rudolph, "Spatially Controlled Adhesion, Spreading, and Differentiation of Endothelial Cells on Self-Assembled Molecular Monolayers, Proceedings of the National Academy of Sciences, 1994, 91, 11070.

Detailed Description Paragraph Type 0 (7):

7) L. A. Chrisey, P. M. Roberts, V. I. Benezra, W. J. Dressick, C. S. Dulcey, and J. M. Calvert, "Selective Attachment of Synthetic DNA to Self-Assembled Monolayer Functionalized Surfaces", Proceedings, Materials Research Society, 1994, 330, 179.

Detailed Description Paragraph Type 0 (9):
9) L. A. Chrisey, G. U. Lee, and C. E. O'Ferrall, "Covalent Attachment of Synthetic DNA to Self-Assembled Monolayer Films", Nucleic Acids Research, 1996, 24, 3031.

Other Reference Publication (5):
Chrisey et al., Selective Attachment of Synthetic DNA to Self-Assembled-Monolayer Functionalized Surfaces, Proceedings, Materials Research Society 330:179-184 (1994).

Other Reference Publication (6):
Chrisey et al., "Covalent Attachment of Synthetic DNA to Self-Assembled Monolayer Films," Nucleic Acids Research 24:3031-3039 (1996).

Other Reference Publication (10):
Dulcey et al., "Photochemistry and Patterning of Self-Assembled Monolayer Films Containing Aromatic Hydrocarbon Functional Groups," Langmuir 12:1638-1650 (1996).

Other Reference Publication (22):
Spargo et al., "Spatially Controlled Adhesion, Spreading, and Differentiation of Endothelial Cells on Self-Assembled Molecular Monolayers," PNAS 91:11070-11074 (1994).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

76. Document ID: US 5980719 A

L24: Entry 76 of 94 File: USPT Nov 9, 1999

US-PAT-NO: 5980719
DOCUMENT-IDENTIFIER: US 5980719 A

TITLE: Electrohydrodynamic receptor
DARE: Invalid display element.

L24: Entry 76 of 94 File: USPT Nov 9, 1999

DOCUMENT-IDENTIFIER: US 5980719 A
TITLE: Electrohydrodynamic receptor

Detailed Description Paragraph Right (71):
FIG. 11 illustrates the bonding of the distribution layer of FIG. 10 to a reservoir layer 1100. Bonding of these sublayers can be achieved through anodic bonding techniques. The three sublayers of the distribution layer are assembled together with a reservoir layer 1100. The reservoir layer contains a pair of electrical connections that are coupled to the sublayer 930 to allow a pair of contacts 1120 to be electrically coupled to electrodes 1012 and 1032. Using these contacts 1120 via an interface module, the EHD micropump on the distribution layer can be activated to dispense fluid from the reservoir 1110.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

77. Document ID: US 5976472 A

L24: Entry 77 of 94 File: USPT Nov 2, 1999

US-PAT-NO: 5976472
DOCUMENT-IDENTIFIER: US 5976472 A

TITLE: Integrated micro-ceramic chemical plant with insertable catalytic reaction chambers

DARE: Invalid display element.

L24: Entry 77 of 94 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5976472 A
TITLE: Integrated micro-ceramic chemical plant with insertable catalytic reaction chambers

Detailed Description Paragraph Right (13):
The permeable partition wall 39a is preferably made by dry pressing ceramic and its composite powders such as zirconia silicate, alumina silicate, zirconia, alumina, silicon carbide, silicon nitride and ceramic composites comprising zirconia-alumina at a pressure such that upon sintering the desired degree of porosity is maintained. It is very important that the pores need to be of the interconnecting variety. The permeable partition wall 39a can also be made alternatively by gel casting, tape casting and injection molding zirconia silicate or alumina silicate such that upon controlled sintering a varying degree of porosity is achieved. The permeable partition wall 39a permits controlled reaction between the chemicals in the fluids on either side of the permeable partition wall 39a to permit the mixing of such fluids during a reaction process. The ceramic powder is blended with polymeric fibers made of materials such as polyvinyl alcohol, polyethylene glycol or acrylic which upon sintering leaves behind interconnected micro-pores. The pore size or the diameter of the sacrificial organic fibers vary in a range from 0.1 to 10 .mu.m because the degree of porosity (density) is warranted by the amount of permeability required for a given chemical process. In other words, custom tailored permeability can be incorporated by controlling the compacting pressure, diameter of the polymer fibers and sintering temperature for a given ceramic composition. The preferred way of making the "green" permeable partition wall containing sacrificial organic fibers such as polyvinyl alcohol, is to gel cast the ceramic mixture containing the organic binders and organic fibers in a mold and air drying the part to drive off the solvent. Upon compacting and subsequent firing the sacrificial organic fibers will produce a wall having a variable degree of porosity. The permeable partition wall 39a, which is in the "green" state, is then incorporated in the unitary ceramic "green" body before all the layers are assembled and sintered to form the sintered unitary micro-ceramic chemical plant. It is instructive to note that a plurality of channels can be provided to handle more than two chemicals or alternatively the catalytic reaction chamber 38 can be made longer by configuring serpentine, complex, wavy, winding and angular meandering forms to allow for longer reaction time. An embedded ceramic heating element 40 is provided in walls defining the perimeter of the chemical delivery chamber 34, the chemical mixing chamber 35, and the reaction/catalytic reaction chamber 38 to provide heat to these chambers. With certain chemical reactions it is particularly important to provide heat to the reaction/catalytic reaction chamber 38. The embedded heating element 40 can be made from ceramics such as MoSi.sub.2, TiB.sub.2, ZrB.sub.2, WO.sub.3 or high-temperature resistive metals or metallic alloys. The electrical leads 41 (see FIG. 3a) for the embedded heating element 40 are located at the side of the second ceramic layer 30 defining the perimeter of the chemical delivery, chemical mixing and reaction/catalytic reaction chambers 34, 35 and 38 respectively and is an integral part thereof. A feedthrough for a thermocouple 42 (see FIG. 3a) located close to the heating element and a thermocouple (not shown) can be inserted in the feedthrough 42 for both monitor and control of temperature of the reaction chamber.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

78. Document ID: US 5965092 A

L24: Entry 78 of 94 File: USPT Oct 12, 1999

US-PAT-NO: 5965092
DOCUMENT-IDENTIFIER: US 5965092 A

TITLE: Integrated micro-ceramic chemical plant with insertable micro-filters
DARE: Invalid display element.

L24: Entry 78 of 94 File: USPT Oct 12, 1999

DOCUMENT-IDENTIFIER: US 5965092 A
TITLE: Integrated micro-ceramic chemical plant with insertable micro-filters

Detailed Description Paragraph Right (13):
The permeable partition wall 39a is preferably made by dry pressing ceramic and its composite powders such as zirconia silicate, alumina silicate, zirconia, alumina, silicon carbide, silicon nitride and ceramic composites comprising zirconia--alumina at a pressure such that upon sintering the desired degree of porosity is maintained. It is very important that the pores need to be of the interconnecting variety. The permeable partition wall 39a can also be made alternatively by gel casting, tape casting and injection molding zirconia silicate or alumina silicate such that upon controlled sintering a varying degree of porosity is achieved. The permeable partition wall 39a permits controlled reaction between the chemicals in the fluids on either side of the permeable partition wall 39a to permit the mixing of such fluids during a reaction process. The ceramic powder is blended with polymeric fibers made of materials such as polyvinyl alcohol, polyethylene glycol or acrylic which upon sintering leaves behind interconnected micro-pores. The pore size or the diameter of the sacrificial organic fibers vary in a range from 0.1 to 10 .mu.m because the degree of porosity (density) is warranted by the amount of permeability required for a given chemical process. In other words, custom tailored permeability can be incorporated by controlling the compacting pressure, diameter of the polymer fibers and sintering temperature for a given ceramic composition. The preferred way of making the "green" permeable partition wall containing sacrificial organic fibers such as polyvinyl alcohol, is to gel cast the ceramic mixture containing the organic binders and organic fibers in a mold and air drying the part to drive off the solvent. Upon compacting and subsequent firing the sacrificial organic fibers will produce a wall having a variable degree of porosity. The permeable partition wall 39a, which is in the "green" state, is then incorporated in the unitary ceramic "green" body before all the layers are assembled and sintered to form the sintered unitary micro-ceramic chemical plant. It is instructive to note that a plurality of channels can be provided to handle more than two chemicals or alternatively the catalytic reaction chamber 38 can be made longer by configuring serpentine, complex, wavy, winding and angular meandering forms to allow for longer reaction time. An embedded ceramic heating element 40 is provided in walls defining the perimeter of the chemical delivery chamber 34, the chemical mixing chamber 35, and the reaction/catalytic reaction chamber 38 to provide heat to these chambers. With certain chemical reactions it is particularly important to provide heat to the reaction/catalytic reaction chamber 38. The embedded heating element 40 can be made from ceramics such as MoSi.sub.2, TiB.sub.2, ZrB.sub.2, WO.sub.3 or high-temperature resistive metals or metallic alloys. The electrical leads 41 (see FIG. 3a) for the embedded heating element 40 are located at the side of the second ceramic layer 30 defining the perimeter of the chemical delivery, chemical mixing and reaction/catalytic reaction chambers 34, 35 and 38 respectively and is an integral part thereof. A feedthrough for a thermocouple 42 (see FIG. 3a) located close to the heating element and a thermocouple (not shown) can be inserted in the feedthrough 42 for both monitor and control of temperature of the reaction chamber.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

79. Document ID: US 5961932 A

L24: Entry 79 of 94 File: USPT Oct 5, 1999

US-PAT-NO: 5961932
DOCUMENT-IDENTIFIER: US 5961932 A

TITLE: Reaction chamber for an integrated micro-ceramic chemical plant
DARE: Invalid display element.

L24: Entry 79 of 94 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5961932 A
TITLE: Reaction chamber for an integrated micro-ceramic chemical plant

Detailed Description Paragraph Right (9):
Referring to FIG. 3, a perspective is illustrated of the second layer from the top 30 wherein contained a reaction chamber 34, a receiving chamber 32 for receiving the raw chemicals from the top layer via the tubes 12 inserted into the inlet holes 13 and a discharge chamber 35 for delivering the chemicals to the next level through the discharge holes 42. The fluids are delivered to opposite sides of the reaction chamber 34 which are separated by a permeable partition wall 36. The permeable partition wall 36 is preferably made by dry pressing ceramic and its composite powders such as zirconia silicate, alumina silicate, zirconia, alumina, silicon carbide, silicon nitride and ceramic composites comprising zirconia-alumina at a pressure such that upon sintering the desired degree of porosity is maintained. The permeable partition wall 36 can also be made alternatively by gel casting, tape casting and injection molding zirconia silicate or alumina silicate such that upon controlled sintering a varying degree of porosity is achieved. The permeable partition wall 36 permits controlled reaction between the chemicals in the fluids on either side of the permeable partition wall 36 to permit the mixing of such fluids during a reaction process. The ceramic powder is blended with polymeric fibers such as polyvinyl alcohol, polyethylene glycol or acrylic which upon sintering leaves behind interconnected micropores. The pore size or the diameter of the sacrificial organic fibers vary in a of range from 0.1 to 10 .mu.m. because the degree of porosity (density) is warranted by the amount of permeability required for a given chemical process. In other words, custom tailored permeability can be incorporated by controlling the compacting pressure, diameter of the polymer fibers and sintering temperature for a given ceramic composition. The preferred way of making the green permeable partition wall 36 containing sacrificial organic fibers such as polyvinyl alcohol, is to gel cast the ceramic mixture containing the organic binders and organic fibers in a mold and air drying the part to drive off the solvent. Upon compacting and subsequent firing the sacrificial organic fibers will produce a wall having a variable degree of porosity. The permeable partition wall 36, which is in the green state, is then incorporated in the unitary ceramic green body before all the layers are assembled and sintered to form the sintered unitary micro-ceramic chemical plant. It is instructive to note that a plurality of channels can be provided to handle more than two chemicals or alternatively the reaction chamber 34 can be made longer by configuring serpentine, complex, wavy, winding and angular meandering forms to allow for longer reaction time. An embedded ceramic heating element 38 is provided in walls defining the perimeter of the reaction chamber 34 to provide heat to the reaction chamber 34. The embedded heating element 38 can be made from ceramics such as MoSi.sub.2, TiB.sub.2, ZrB.sub.2, or high-temperature resistive metals or metallic alloys. The electrical leads 40 for the embedded heating element 38 are located at the side of the ceramic second layer 30 defining the perimeter of the reaction chamber 34, and is an integral part thereof. The reaction chamber 34 leads to discharge holes 42 contained in the discharge chamber 35 which merges into the next layer 100. The cross-section of the reaction chamber 34 is configured as a rectangle but can be of other shapes such as oval, circular, triangular or any other convenient cross-section. The discharge holes 42 are directly connected to a receiving channel 60 in the next layer 100.

80. Document ID: US 5961930 A

L24: Entry 80 of 94 File: USPT Oct 5, 1999

US-PAT-NO: 5961930
DOCUMENT-IDENTIFIER: US 5961930 A

TITLE: Integrated micro-ceramic chemical plant with insertable reaction chambers and micro-filters

DARE: Invalid display element.

L24: Entry 80 of 94 File: USPT Oct 5, 1999

DOCUMENT-IDENTIFIER: US 5961930 A
TITLE: Integrated micro-ceramic chemical plant with insertable reaction chambers and micro-filters

Detailed Description Paragraph Right (13):
The permeable partition wall 39a is preferably made by dry pressing ceramic and its composite powders such as zirconia silicate, alumina silicate, zirconia, alumina, silicon carbide, silicon nitride and ceramic composites comprising zirconia-alumina at a pressure such that upon sintering the desired degree of porosity is maintained. It is very important that the pores need to be of the interconnecting variety. The permeable partition wall 39a can also be made alternatively by gel casting, tape casting and injection molding zirconia silicate or alumina silicate such that upon controlled sintering a varying degree of porosity is achieved. The permeable partition wall 39a permits controlled reaction between the chemicals in the fluids on either side of the permeable partition wall 39a to permit the mixing of such fluids during a reaction process. The ceramic powder is blended with polymeric fibers made of materials such as polyvinyl alcohol, polyethylene glycol or acrylic which upon sintering leaves behind interconnected micro-pores. The pore size or the diameter of the sacrificial organic fibers vary in a range from 0.1 to 10 .mu.m because the degree of porosity (density) is warranted by the amount of permeability required for a given chemical process. In other words, custom tailored permeability can be incorporated by controlling the compacting pressure, diameter of the polymer fibers and sintering temperature for a given ceramic composition. The preferred way of making the "green" permeable partition wall containing sacrificial organic fibers such as polyvinyl alcohol, is to gel cast the ceramic mixture containing the organic binders and organic fibers in a mold and air drying the part to drive off the solvent. Upon compacting and subsequent firing the sacrificial organic fibers will produce a wall having a variable degree of porosity. The permeable partition wall 39a , which is in the "green" state, is then incorporated in the unitary ceramic "green" body before all the layers are assembled and sintered to form the sintered unitary micro-ceramic chemical plant. It is instructive to note that a plurality of channels can be provided to handle more than two chemicals or alternatively the catalytic reaction chamber 38 can be made longer by configuring serpentine, complex, wavy, winding and angular meandering forms to allow for longer reaction time. An embedded ceramic heating element 40 is provided in walls defining the perimeter of the chemical delivery chamber 34, the chemical mixing chamber 35, and the reaction/catalytic reaction chamber 38 to provide heat to these chambers. With certain chemical reactions it is particularly important to provide heat to the reaction/catalytic reaction chamber 38. The embedded heating element 40 can be made from ceramics such as MoSi.sub.2, TiB.sub.2, ZrB.sub.2, WO.sub.3 or high-temperature resistive metals or metallic alloys. The electrical leads 41 (see FIG. 3a) for the embedded heating element 40 are located at the side of the second ceramic layer 30 defining the perimeter of the chemical delivery, chemical mixing and reaction/catalytic reaction chambers 34, 35 and 38 respectively and is an integral part thereof. A feedthrough for a thermocouple 42 (see FIG. 3a) located close to the heating element and a thermocouple (not shown) can be inserted in the feedthrough 42 for both monitor and control of temperature of the reaction chamber.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

81. Document ID: US 5955379 A

L24: Entry 81 of 94 File: USPT Sep 21, 1999

US-PAT-NO: 5955379
DOCUMENT-IDENTIFIER: US 5955379 A

TITLE: Biosensor device and method
DARE: Invalid display element.

L24: Entry 81 of 94 File: USPT Sep 21, 1999

DOCUMENT-IDENTIFIER: US 5955379 A
TITLE: Biosensor device and method

Detailed Description Paragraph Right (47):
Where the heterodimer is embedded in a hydrocarbon-chain monolayer, as described below, the spacer anchoring the HSP1 peptide to the biosensor surface may be a hydrocarbon chain. The chain is preferably a fractional length of the chains making up the bilayer, such that the distal ends of the heterodimer peptides in the assembled monolayer are at or near the exposed surface of the monolayer. Thus, for example, if the monolayer is made up of 18-carbon chains, the spacer is preferably 2-10 carbons in length, depending on the length of the assembled heterodimer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

82. Document ID: US 5952172 A

L24: Entry 82 of 94 File: USPT Sep 14, 1999

US-PAT-NO: 5952172
DOCUMENT-IDENTIFIER: US 5952172 A

TITLE: Nucleic acid mediated electron transfer
DARE: Invalid display element.

L24: Entry 82 of 94 File: USPT Sep 14, 1999

DOCUMENT-IDENTIFIER: US 5952172 A
TITLE: Nucleic acid mediated electron transfer

Other Reference Publication (20):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces", J. Am. Chem. Soc. 117:9529-9534 (1995).

Other Reference Publication (26):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research 24(15):3031-3039 (1996).

Other Reference Publication (38):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers", J. Am. Chem. Soc. 112:4301-4306 (1990).

Other Reference Publication (50):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem. 68(3):490-497 (1996).

Other Reference Publication (89):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem, 68(3):490-497 (1996).

Other Reference Publication (96):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .alpha.-.omega.-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces," J. Am. Chem. Soc., 117:9529-9534 (1995).

Other Reference Publication (100):
Uosake, K., et al., "A Self-Assembled Monolayer of Ferrocenylalkane Thiols on Gold as an Electron Mediator for the Reduction of Fe(III)-EDTA in Solution," Electrochemica Acta., 36(11/12):1799-1801 (1991).

Other Reference Publication (118):
Sato, Y., et al., "Unidirectional Electron Transfer at Self-Assembled Monolayers of 11-Ferrocenyl-1-undecanethiol on Gold," Bull. Chem. Soc. Jpn., 66(4):1032-1037 (1993).

Other Reference Publication (158):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films," Nucleic Acids Research, 24(15):3031-3039 (1996).

Other Reference Publication (183):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers," J. Am. Chem. Soc., 112:4301-4306 (1990).

83. Document ID: US 5938904 A

L24: Entry 83 of 94 File: USPT Aug 17, 1999

US-PAT-NO: 5938904
DOCUMENT-IDENTIFIER: US 5938904 A

TITLE: Separation of charged particles by a spatially and temporally varying electric field

DARE: Invalid display element.

L24: Entry 83 of 94 File: USPT Aug 17, 1999

DOCUMENT-IDENTIFIER: US 5938904 A
TITLE: Separation of charged particles by a spatially and temporally varying electric field

Detailed Description Paragraph Right (116):
A second alternative method suitable for Au uses microcontact printing (.mu.CP) (Xia et al., 1995, J. Am. Chem. Soc. 117:3274-3275; Jackman et al., 1995, Science 269:664-666). Instead of a photolithography mask, an elastomeric stamp made according to an identical pattern of the same dimensions is used. FIGS. 16A-B illustrate exemplary patterns. The stamp can be fabricated from polydimethylsiloxane. As before, Au is deposited to a thickness of 1 .mu.m on the surface of the substrate using standard methods. Next, the elastomeric stamp is wetted with an alkanethiol and pressed against the gold surface. A suitable alkanethiol is CH.sub.3 (CH.sub.2).sub.15 SH (Kumar et al., 1994, Langmuir 10:1498-1511). Controlled spreading of the patterned self-assembled alkanethiol monolayer on the gold surface can be achieved by performing the printing under water, which has the further benefit of shrinking the feature size in a predictable manner. The stamp and substrate are removed from the water and dried using N.sub.2 gas, and then the stamp is removed from the substrate. Unprotected gold is removed by immersion in a cyanide solution (0.1M KCN, 1M KOH) with vigorous stirring using air or oxygen as an oxidant (Kumar et al., supra.). After a good rinse, the alkanethiol is removed from the surface to yield the pluralities of gold electrodes.

84. Document ID: US 5849208 A

L24: Entry 84 of 94 File: USPT Dec 15, 1998

US-PAT-NO: 5849208
DOCUMENT-IDENTIFIER: US 5849208 A

TITLE: Making apparatus for conducting biochemical analyses
DARE: Invalid display element.

L24: Entry 84 of 94 File: USPT Dec 15, 1998

DOCUMENT-IDENTIFIER: US 5849208 A
TITLE: Making apparatus for conducting biochemical analyses

Detailed Description Paragraph Right (31):
The groove center 180c is positioned a distance 162 from side 124b and a distance 164 from side 124a. Thus, when the layers of the substrate are assembled a thermocouple wire 182 installed in the groove 180 will be positioned in thermal contact with the center 160 of the reaction chamber floor 143 positioned in upper polyimide layer 122. The thermocouple wire 182 has ends 182a and 182b which terminate at or about side 124b and may connected to external circuitry by conventional means.

Detailed Description Paragraph Right (38):
The strips have interconnect pads 252a and 254a positioned at side 224b for connecting to an external power source. The interconnect pads can be positioned at any side or surface and may include conventional means for connecting to external circuitry. The strips also have fluid interface pads 252b and 254b. Both fluid pads are positioned a distance 272 from side 224b. Pad 252b is positioned a distance 274 from side 224a and pad 254b is positioned a distance 276 from pad 252a. Thus, when the layers of the substrate are assembled together, the fluid interface pad 252b is positioned directly beneath hole 270a and fluid interface pad 254b is positioned beneath hole 270b. A current path is provided between the fluid interface pads when the reaction chamber 240 is filled with fluid and the fluid is heated by the electrical resistance of the fluid as current is transmitted therethrough. The terminal strips are preferably formed of copper. Fluid pads 252b and 254b are preferably plated with a corrosion-resistant material such as platinum.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

85. Document ID: US 5847019 A

L24: Entry 85 of 94 File: USPT Dec 8, 1998

US-PAT-NO: 5847019
DOCUMENT-IDENTIFIER: US 5847019 A

TITLE: Photoactivatable polymers for producing patterned biomolecular assemblies
DARE: Invalid display element.

L24: Entry 85 of 94 File: USPT Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5847019 A
TITLE: Photoactivatable polymers for producing patterned biomolecular assemblies

Other Reference Publication (10):
Prime et al., "Adsorption of Proteins onto Surfaces Containing End-Attached Oligo(ethylene oxide): A Model System Using Self-Assembled Monolayers", J. Am. Chem. Soc'y. 115 10714-21 (1993).

Other Reference Publication (11):
Pale-Grosdemange et al., "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo(ethylene glycol) of Structure HS(CH.sub.2).sub.11 (OCH.sub.2).sub.m OH on Gold", J. Am. Chem. Soc'y 113 12-20 (1993).

Other Reference Publication (12):
Lopez et al., "Scanning Electron Microscopy Can Form Images of Patterns in Self-Assembled Monolayers", Langmuir 9 1513-16 (1993).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

86. Document ID: US 5824473 A

L24: Entry 86 of 94 File: USPT Oct 20, 1998

US-PAT-NO: 5824473
DOCUMENT-IDENTIFIER: US 5824473 A

TITLE: Nucleic acid mediated electron transfer
DARE: Invalid display element.

L24: Entry 86 of 94 File: USPT Oct 20, 1998

DOCUMENT-IDENTIFIER: US 5824473 A
TITLE: Nucleic acid mediated electron transfer

Other Reference Publication (48):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, .rho.-.rho.-Dithiols, and Thioacetyl-Containing Absorbates. Understanding Attachments

between Potential Molecular Wires and Gold Surfaces", J. Am. Chem. Soc. 117:9529-9534 (1995).

Other Reference Publication (61):
Chrisey et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research 24(15) :3031-3039 (1996).

Other Reference Publication (73):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers", J. Am. Chem. Soc. 112:4301-4306 (1990.

Other Reference Publication (85):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem. 68(3) :490-497 (1996).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

87. Document ID: US 5770369 A

L24: Entry 87 of 94 File: USPT Jun 23, 1998

US-PAT-NO: 5770369
DOCUMENT-IDENTIFIER: US 5770369 A

TITLE: Nucleic acid mediated electron transfer
DARE: Invalid display element.

L24: Entry 87 of 94 File: USPT Jun 23, 1998

DOCUMENT-IDENTIFIER: US 5770369 A
TITLE: Nucleic acid mediated electron transfer

Other Reference Publication (61):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, --Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces", J. Am. Chem. Soc. 117:9529-9534 (1995).

Other Reference Publication (67):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research 24(15):3031-3039 (1996).

Other Reference Publication (78):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold Electroactive Self-Assembled Monolayers", J. Am. Chem. Soc. 112:4301-4306 (1990).

Other Reference Publication (90):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem. 68(3):490-497 (1996).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

☒ 88. Document ID: US 5736257 A

L24: Entry 88 of 94 File: USPT Apr 7, 1998

US-PAT-NO: 5736257
DOCUMENT-IDENTIFIER: US 5736257 A

TITLE: Photoactivatable polymers for producing patterned biomolecular assemblies
DARE: Invalid display element.

L24: Entry 88 of 94 File: USPT Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736257 A
TITLE: Photoactivatable polymers for producing patterned biomolecular assemblies

Other Reference Publication (7):
Prime et al., "Adsorption of Proteins onto Surfaces Containing End-Attached Oligo(ethylene oxide): A Model System Using Self-Assembled Monolayers", J. Am. Chem. Soc., 115, pp. 10714-10721, 1993.

Other Reference Publication (8):
Pale-Grosdemange et al., "Formation of Self-Assembled Monolayers by Chemisorption of Derivatives of Oligo(ethylene glycol) of Structure HS(CH.sub.2).sub.11 (OCH.sub.2 CH.sub.2).sub.m OH on Gold", J. Am. Chem. Soc., 113, pp. 12-20, 1991.

Other Reference Publication (9):
Lopez et al. "Scanning Electron Microscopy Can Form Images of Patterns in Self-Assembled Monolayers", Langmuir, vol. 9, pp. 1513-1516, 1993.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

☐ 89. Document ID: US 5705348 A

L24: Entry 89 of 94 File: USPT Jan 6, 1998

US-PAT-NO: 5705348
DOCUMENT-IDENTIFIER: US 5705348 A

TITLE: Nucleic acid mediated electron transfer
DARE: Invalid display element.

L24: Entry 89 of 94 File: USPT Jan 6, 1998

DOCUMENT-IDENTIFIER: US 5705348 A
TITLE: Nucleic acid mediated electron transfer

Other Reference Publication (4):
Tour, et al., "Self-Assembled Monolayers and Multilayers of Conjugated Thiols, p-p-Dithiols, and Thioacetyl-Containing Adsorbates. Understanding Attachments between Potential Molecular Wires and Gold Surfaces", J. Am. Chem. Soc. 117:9529-9534 (1995).

Other Reference Publication (10):
Chrisey, et al., "Covalent attachment of synthetic DNA to self-assembled monolayer films", Nucleic Acids Research 24(15):3031-3039 (1996).

Other Reference Publication (22):
Chidsey, et al., "Coadsorption of Ferrocene-Terminated and Unsubstituted Alkanethiols on Gold" Electroactive Self-Assembled Monolayers J. Am. Chem. Soc. 112:4301-4306 (1990).

Other Reference Publication (34):
Sigal et al., "A Self-Assembled Monolayer for the Binding and Study of Histidine-Tagged Proteins by Surface Plasmon Resonance," Anal. Chem. 68(3):490-497 (1996).

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

90. Document ID: US 5677195 A

L24: Entry 90 of 94 File: USPT Oct 14, 1997

US-PAT-NO: 5677195
DOCUMENT-IDENTIFIER: US 5677195 A

TITLE: Combinatorial strategies for polymer synthesis
DARE: Invalid display element.

L24: Entry 90 of 94 File: USPT Oct 14, 1997

DOCUMENT-IDENTIFIER: US 5677195 A
TITLE: Combinatorial strategies for polymer synthesis

Detailed Description Paragraph Right (95):
Methods for controlling chemical composition and therefore the local surface free energy of a substrate surface include a variety of techniques apparent to those skilled in the art. Chemical vapor deposition and other techniques applied in the fabrication of integrated circuits can be applied to deposit highly uniform layers on selected regions of a surface. As a specific example, the wettability of a silicon wafer surface has been manipulated on the micrometer scale through a combination of self-assembled monolayer depositions and micromachining. See Abbott et al., "Manipulation of the Wettability of Surfaces on the 0.1 to 1 Micrometer Scale Through Micromachining and Molecular Self-Assembly" Science, 257 (Sep. 4, 1992) which is incorporated herein by reference for all purposes.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

91. Document ID: US 5597457 A

L24: Entry 91 of 94 File: USPT Jan 28, 1997

US-PAT-NO: 5597457
DOCUMENT-IDENTIFIER: US 5597457 A

TITLE: System and method for forming synthetic protein crystals to determine the conformational structure by crystallography
DARE: Invalid display element.

L24: Entry 91 of 94 File: USPT Jan 28, 1997

DOCUMENT-IDENTIFIER: US 5597457 A
TITLE: System and method for forming synthetic protein crystals to determine the conformational structure by crystallography

Detailed Description Paragraph Right (8):
In general, proteins should orient themselves at the electrode surfaces in the presence of strong electric fields generated in a compact layer, e.g., 10.sup.8 V/m., due to dipole orientation. However, there can be chemical interactions between the electrode surface and the protein that impact the orientation and therefore the whole synthesis of a quality crystal. For example, sulfur-containing molecules, such as thiols, often show strong adsorption on a gold electrode, and self-assembly of monolayers has been observed based upon this interaction. Such interactions may exceed the field-induced forces that act on the molecular dipoles.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

92. Document ID: US 5589136 A

L24: Entry 92 of 94 File: USPT Dec 31, 1996

US-PAT-NO: 5589136
DOCUMENT-IDENTIFIER: US 5589136 A

TITLE: Silicon-based sleeve devices for chemical reactions
DARE: Invalid display element.

L24: Entry 92 of 94 File: USPT Dec 31, 1996

DOCUMENT-IDENTIFIER: US 5589136 A
TITLE: Silicon-based sleeve devices for chemical reactions

Detailed Description Paragraph Right (49):
The ECL microcell, as described in greater detail hereinafter with respect to FIGS. 21-31, is a multilayer assembly of micromachined silicon and glass. Cells with solution capacity ranging from 35 .mu.L to 85 .mu.L have been designed and fabricated in silicon. An e-beam deposited, gold, thin film forms the cell cathode. The anode is also a thin film. Experiments with both indium tin oxide (ITO) and platinum have been carried out. ITO is transparent to visible light, so that when deposited onto glass, it can form the top layer of the assembly, through which the emitted light can be picked up by a photodetector (see FIG. 21). The assembly also contains micromachined fluid fill ports (see FIG. 22). The layers were assembled and bonded together (see FIGS. 29-30) using a low temperature curing polyimide, such as Epotek 400.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC
Draw Desc | Image

93. Document ID: US 4988421 A

L24: Entry 93 of 94 File: USPT Jan 29, 1991

US-PAT-NO: 4988421

DOCUMENT-IDENTIFIER: US 4988421 A

TITLE: Method of toughening diamond coated tools
DARE: Invalid display element.

L24: Entry 93 of 94 File: USPT Jan 29, 1991

DOCUMENT-IDENTIFIER: US 4988421 A
TITLE: Method of toughening diamond coated tools

Detailed Description Paragraph Right (46):
The binding material is applied to the diamond particle/tool assembly by the process of magnetron sputtering at ambient temperature conditions from a target of molybdenum. A film 51 of approximately 10 microns is applied to the tool (as shown schematically in FIG. 3). Following deposition of the metal layer, the assembly is reheated to deposit another layer of Particles by CVD and again cooled to ambient to carry out PVD at ambient conditions. This was repeated to provide two layers each of the particles and binding material. Each time CVD was carried out following PVD of Mo, the initial stage of CVD converts the exposed surface of Mo to molybdenum carbide by preferential absorption of carbon from the chemical vapor prior to the formation of any diamond particles. The total thickness of the deposited layers, both particles and binding material, will be thicker than any coating ever contemplated or ever deposited by the prior art; the multiple layer will be about 50-125 microns, and should be at least 15 microns as a minimum.

94. Document ID: US 4259433 A

L24: Entry 94 of 94 File: USPT Mar 31, 1981

US-PAT-NO: 4259433
DOCUMENT-IDENTIFIER: US 4259433 A

TITLE: Method for producing disk-recording plates
DARE: Invalid display element.

L24: Entry 94 of 94 File: USPT Mar 31, 1981

DOCUMENT-IDENTIFIER: US 4259433 A
TITLE: Method for producing disk-recording plates

CLAIMS:

1. A method for producing a disc-recording plate from a composite layer consisting of a substrate, an etching layer having a thickness of 1000 to 1500 A overlying said substrate and a laser-sensitive layer having a thickness of 200 to 500 A overlying said etching layer, wherein the said laser-sensitive layer is composed of a material selected from the group consisting of Au, Cu, Cr, Ni, Co, Pt, Pd, Ir, Rh and stainless steel, and wherein the etching layer is easily etched by a reactive sputter-etching treatment in an inert atmosphere of a halogenated hydrocarbon and the laser-sensitive layer has a resistance to the reactive sputter etching in said atmosphere of halogenated hydrocarbon, said method comprising: exposing the assembly to the irradiation of laser beams to selectively remove the laser-sensitive layer, and then subjecting the assembly to the reactive sputter-etching treatment in the atmosphere of the halogenated hydrocarbon under a pressure of 10.sup.-3 to 10.sup.-1 Torr to remove

the etching layer at portions corresponding to the removed portions of the laser-sensitive layer.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | KWIC | Draw Desc | Image

Generate Collection | Print

Terms	Documents
117 not 119	94

Display Format: TI, DAR Change Format

Previous Page Next Page